The American Journal of Human Genetics

Vol. 9 No. 4 *December 1957*

The Cunier Pedigree of "Color Blindness"

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THE FIVE-GENERATION PEDIGREE which Florent Cunier published in 1839 (and only then; see Appendix A) has held the attention of geneticists for as long as there has been genetics. The inheritance of the most familiar kinds of color blindness is clearly X-linked and recessive, so that a color-blind woman married to a color-normal man has daughters who are all normal like her husband, and sons who are all color blind like herself. The color defect in Cunier's kindred was transmitted from affected mothers to all of their daughters but to none of their sons (Figure 1).

The Cunier pedigree was taken at face value by all for nearly a century (and still is, by most people), as exhibiting an extraordinary inheritance of ordinary color blindness. The X-linkage of the common color blindnesses was recognized as early as 1911 (by T. H. Morgan and by E. B. Wilson), but not firmly established until the 1920's. Meanwhile, factors were at work to keep the Cunier pedigree from coming under any sort of suspicion.

Types and subtypes of color blindness were still being discovered or discriminated from already-known conditions well into the twentieth century (tritanomaly, tetartanopia, atypical achromasy), and long after Cunier even a single odd case would readily be accepted as "belonging", as the prototype of a new category. The inheritance of the color blindnesses was imperfectly known, and did not appear to be any too rigid owing to such phenomena as manifesting heterozygotes, the occurrence of two kinds of non-allelic defects in the same family, etc. Most of the writers who dealt with the Cunier pedigree were interested only in the "color blindness." With each one copying from others and with no-one going back to Cunier's original words, there rapidly faded from the literature, by 1920, practically all mention of any defects in Cunier's females other than the color-visual one. With the latter supposed to be "ordinary", its female-to-female transmission seemed unusual and interesting, but it could not very well be branded impossible. It was easy for the Cunier color defect to descend through generations of books without its genuineness being questioned. (*Mea quoque culpa!* C.S. And with my "help." G.L.W.).

It is interesting to note the position of the Cunier pedigree, as evaluated by one color-blindness authority about half-way from Cunier's time to the 1920's, and by another at the threshold of the critical decade.

When he wrote his important book in 1880, B. Joy Jeffries had only just swung

Received March 25, 1957.

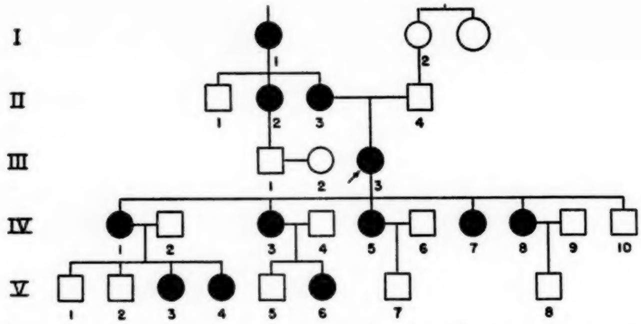

FIGURE 1. THE CUNIER PEDIGREE OF "COLOR BLINDNESS." (True birth orders in generations II and V are not known, nor is the true position of "IV-10" in his sibship. Birth order *was* as shown for the females of generation IV, *inter se*).

around to the view that color blindness is *less* common in females than in males. He found himself forced to admit that no color-blind can be cured by exercises with colors, but he believed nevertheless that the more extensive practice women had with colored materials (in various kinds of "fancy work") could affect their female offspring differentially, tending to compensate for any color blindness in *them*. Jeffries' knowledge of the Cunier pedigree was, typically, second-hand. He did not list Cunier in his huge bibliography, and from his wording it is at once obvious that his description was a direct translation from the French of Élie Wartmann (1849). Jeffries exactly reproduced Wartmann's careless errors, including the monstrous one of giving the proposita two affected sisters and a normal brother, whereas she was an only child (Figure 1). He did not suspect that the Cunier defect might be something physiologically unique, and he did not know that the same females in the family shared and monopolized other peculiarities. The biggest impression the pedigree made on Jeffries was this:

> "We thus have the remarkable instance of color-blindness appearing *only* in the *females* of a family for four generations. Heredity has here apparently acted without reference to, or directly against, the accumulated effects of generations of exercise with colors. It is certainly a very curious fact, that, if generations of exercise with colors is gradually eliminating color-blindness from females, this should not have checked its transmission through females exclusively for four generations."

The position of the Cunier pedigree in 1920 is well displayed in that most massive compendium of ophthalmological information, the Graefe-Saemisch *Handbuch der gesamten Augenheilkunde*. Groenouw, who had been entrusted with the genetical section of the second edition in 1901, was still the best available authority on heredity-in-ophthalmology when the third and last edition was being planned. In his account, finished in 1915 but not actually published until 1920, he accepted the Cunier females as having ordinary "red-green blindness" and knew of nothing else being wrong with them. While he could not cite any other all-female red-green-blind families by chapter and verse, he would not have been surprised at their turning up around him, for he

said that: "There are families in which along with men, women are also affected, very rarely women alone."

Within a year or two this position was being shaken. Writers who had compiled enough old and new pedigrees to see how the X-chromosomal color defects really are inherited Döderlein (1921), Schiötz (1922), Bell (1926), Just (1934), and others—sought to avoid embarrassment from the Cunier pedigree by attacking its reliability, by questioning the comparability of its color defect with "true" hereditary color blindness, and by resurrecting information (almost always second-hand) suggesting that the eyes of Cunier's females were substantially pathological, with disturbance of color vision as a subsidiary effect.

Schiötz went too far in asserting that the women had serious visual deterioration, for Cunier had not said anything that should indicate any such thing to a modern oculist. Even so, such exaggeration would really have been a good thing if it had promoted skepticism and led more people to go back to Cunier's own words. But, such skepticism as there was during the 1920's was not infectious enough—at least, it did not spread among geneticists, as will shortly be apparent. There was indeed one man who was very close to what we think was the truth (and perhaps before 1920). This was C. H. Usher, who communicated his ideas to Bell, who gave them favorable mention (Bell, 1926). Like Bell herself, he believed that the eyes had some pathological condition to which the color defect was secondary, and Usher thought this to be a lens defect.

The first *ad hoc* genetical explanation of hologynic inheritance in modern cytologic terms was offered by Enriques (1922). He suggested that females have an "Ff" pair of chromosomes (males, "ff"), and that the Cunier "daltonism" factor was in the "F." To ensure that "F" would never get into a male, he hypothesized selective fertilization: "F" eggs could receive only X-bearing, "f" eggs only Y-bearing, sperms.

Where Groenouw had supposed that in some families red-green color blindness is dominant, and even his critic Döderlein thought that deuteranomaly, at least, is dominant, rather more sophisticated hypotheses involving dominance were offered for the Cunier pedigree. These avoided the question of whether the color defect was an "ordinary" (familiar) one which ought always to be recessive and ought usually to show in males only. Gates (1923), Castle (1930), and Haldane (1932) proposed a dominant mutation, producing color blindness, and either lethal in the male or with the effect (or the transmissability) of the allele absent in males. Another mechanism suggested by Haldane was an extranuclear factor (familiar from plant genetics), with its action limited to the female sex.

Such suggestions have not been followed up. Instead, a very different explanation has found general favor. In 1922 L. V. Morgan published on a situation she had found in Drosophila, where a well-known X-linked trait was not transmitted as usual by a homozygous recessive mother to all of her sons and none of her daughters, but on the contrary to all daughters and no sons. Besides establishing this mode of inheritance, Morgan provided a complete explanation of it in terms of a "new" kind of chromosome. She showed that the females in the strain had a single large V-shaped X-element which had apparently originated by the attachment to each other, at one end, of normally separate rod-shaped X-chromosomes. These "attached X-chromo-

somes" behaved as a unit in transfer from one generation to the next, every female receiving them (and the homozygous-recessive genotype) from the mother and a Y-chromosome from her father, and every male receiving an X-chromosome from the father and a Y from his mother.

T. H. Morgan, in a laboratory conversation with one of us (C.S.; in the 1924–6 period), pointed out that attached X-chromosomes could have been the cause of the peculiar transmission of color blindness in Cunier's material. In 1927, Enriques made just such a suggestion—but as a pure hypothesis. He had no knowledge of Mrs. T. H. Morgan's discovery, but thought non-disjunction of X-chromosomes (somehow made *permanent*) more plausible as an explanation of the Cunier pedigree than the scheme he had hypothesized five years earlier. Later, the attached-X hypothesis was offered by several workers (independently of each other) who did know of L. V. Morgan's discovery (Levit and Serebrovsky, 1929; Haldane, 1932, Gowen, 1933). Haldane cited not only Cunier's, but five other pedigrees (one of them non-existent—see Appendix B), involving various diseases in which exclusive and complete transmission down the direct female line was said to have occurred. He regarded all of them as evidence for attached X-chromosomes in Man. Levit (1934), however, pointed out that all "five" pedigrees showed features at variance with the hypothesis. In two, not all of the daughters were like their mothers, and in the other three there was insufficient evidence that the traits concerned are ordinarily X-linked in the first place. According to Levit, no known kindred besides Cunier's fulfills these two necessary conditions for an interpretation in terms of attached X-chromosomes. On the other hand Just (1934) singled out the Cunier pedigree, from among Haldane's six, for special criticism. He took Schiötz's word for it that Cunier's females had seriously pathological eyes and vision, and not "the usual red-green blindness"; and, although he made no reference to Döderlein, he thought (like the latter) that very old information is automatically unreliable, and he questioned whether one should try to fit *any* special genetical hypothesis to it.

Sorsby's explanation of the Cunier pedigree is at first glance apparently distinct from the attached-X one (Sorsby, 1951, p. 30, pp. 43–44). It is in terms of non-disjunction. No mechanism but attachment is known, that produces 100% non-disjunction. There is good reason to think however, particularly from his Fig. 15 and the neighboring letterpress, that by non-disjunction Sorsby really meant physical attachment. By "non-disjointed X chromosome" on his p. 30 (and also by "disjointed X chromosome" on his p. 44!) he seems to have meant attached X-chromosomes in the Morgan sense.

The mechanisms by which "new" chromosomes (whether sex chromosomes or not) originate need to be understood before attached X-chromosomes can be discussed in the required detail. Numerous studies in various species of both animals and plants have revealed three such mechanisms, any one of which suffices:

1) Crossing-over, which if it occurs at corresponding sites in two morphologically identical chromosomes produces nothing visibly new, but which if "unequal" (as described below) yields obviously new complexes.

2) Breakage, with rejunction that does not restore the *status quo ante*. If two or more breaks occur (not necessarily in the same chromosome), and broken ends fuse

so as to combine in contiguity segments formerly separated, new chromosomes result.

3) Misdivision of the kinetochore. Whereas normally a chromosome with arms "A" and "B" yields two "AB" sister chromosomes, the kinetochore may so divide that one sister kinetochore joins two "A" arms and the other unites two "B" arms.

Attached X-chromosomes are the one kind of new chromosomes with which we need concern ourselves here. The complexity of attached-X phenomena described to date in *Drosophila* (L. V. Morgan, 1938; Novitski, 1954) must be set forth before the thought of possible origin and transmission of attached X's in Man is even entertained. From the listing of mechanisms above, it is clear that two X-chromosomes do not become attached merely by being spot-welded to each other at some point.

In *D. melanogaster*, an X has a long arm and a very short arm. In such a (*normal*) X, the polarity of each arm is conventionally indicated by calling the kinetochore end proximal and the other end distal, these labels adhering to the chromatin even if inversion should occur.

The classical type of attached-X complex lacks the two short arms and contains only the two long ones, joined at their proximal ends. These V's originate by way of very rare cross-over events. In a relatively simple process, the short arm of one X and the long arm of the other may be involved. A more complicated two-stage process begins with crossing-over between the long arm of the X and one of the arms of the Y-chromosome, thus producing an X whose short arm is replaced by one of the arms of the Y ("$\widehat{\mathrm{XY}}$"). In a stock of such flies there may later occur (as a separate rarity) crossing-over between the X arm of the one $\widehat{\mathrm{XY}}$ and the Y arm of the other $\widehat{\mathrm{XY}}$. The resulting V-shaped attached X-chromosome is called "reversed metacentric"—metacentric because its kinetochore is located in its middle; "reversed" because the two arms of the V are disposed with respect to the kinetochore so that the sequence of regions may be listed as "distal → proximal/kinetochore/proximal → distal." The two possible modes of origin of these reversed metacentric complexes make the regions near the kinetochore, in some of them, to come from the short arm of the X whereas in others the kinetochore and the neighboring parts are derived from the Y-chromosome.

The occurrence of crossing-over between the proximal regions of the long and short arms of an X, or between the long arm and either arm of a Y, suggests that all four proximal regions are equivalent in content ("homologous"). If they are, then a female with two free X-chromosomes possesses four doses of this chromosomal material whereas a reversed metacentric attached X-chromosome has only two doses, the other two having been removed in meiotic segregation.

In addition to the reversed metacentric, five other main types of attached X-chromosomes are now known (see Novitski, 1954). Three of these embody inversions, and are "tandem metacentrics" (*e.g.*, distal → proximal/kinetochore/distal → proximal), reversed "acrocentrics", and tandem acrocentrics. Acrocentric here means that the two arms are extremely unequal in length, the very short arm being that of a normal X-chromosome, and the very long one consisting of the long arms of two X-chromosomes, joined end-to-end. The other two classes are ring chromosomes,

reversed and tandem, which can originate from certain of the above. All these compounds result from what has been called unequal crossing-over, *i.e.*, crossing-over between regions homologous in content but topographically non-correspondent.

The ring compounds lack the two short arms of two free X-chromosomes, just as do the metacentrics. The acrocentrics lack only one of them.

The origin of the reversed acrocentric, as well as that of some of the other compounds, involves the prior existence in the population of free X-chromosomes in which nearly the entire long arm has been inverted relative to the standard arrangement, with perhaps a part of a Y-chromosome also attached to the free end of the long arm.

The formation of attached-X complexes in *Drosophila* depends upon a single rare event or even a particular sequence of different events each rare in itself. Moreover, only three of the six possible compounds—the reversed ones—are stable since the tandem types produce single chromosomes by typical, equal, crossing-over. No wonder, then, that attached X-chromosomes have been found only in laboratories, even though the survival of wild flies bearing such chromosomes would be possible since the short arms of the X-chromosomes, for which attached-X compounds are deficient, are of small viability value if any.

In contrast to *Drosophila*, the two arms of the human X-chromosome are both of appreciable (though unequal) length. Nothing definite is known about their homology, but it appears that essential differences exist between the two arms (Kodani, 1957). If attached X-chromosomes occur in Man, and if they originate in any such way(s) as in *Drosophila*, then they would consist of two arms homologous *inter se* (from two free X-chromosomes), plus at most one other arm, the absent arm(s) having segregated from those present (barring non-disjunction, which may be superimposed upon any of the three mechanisms listed above). Even though the shorter arm of the X may be largely heterochromatic, it may be assumed that all four arms would be required for full development of a female zygote.

Any detailed pursuit of the hypothetical modes of origin of attached X-chromosomes in Man would be fruitless—so many mechanisms, with variations on each theme, could be postulated. *Drosophila* may seem to offer bewildering variety; but, be it remembered, *Drosophila* is only one of many organisms in which various kinds of chromosome attachments are known to occur, and these always form in a complicated manner.

It should be apparent that expectations about the possibility of, and behavior of, attached X-chromosomes in Man do not follow in a simple fashion from a simple situation in *Drosophila*, for things there are far more complicated than they were thought to be by those who first offered the attached-X hypothesis in explanation of the Cunier pedigree.

The present paper is an attempt at a definitive re-examination of Cunier's article. It is necessarily lengthy; but, it is high time that more of the details, and more of an exegesis, both of the original story and the "explanations", were given place in a single discussion. Past treatments of the Cunier pedigree have been so skimpy that they were sure to mislead both ophthalmologists who knew little genetics and geneti-

cists who knew little ophthalmology. The very few investigators who are each an excellent geneticist, and at the same time an excellent visual scientist, have not happened to concern themselves with the Cunier puzzle.

If we are to be definitive, we must deal with several questions. Are the facts reported in it reliable? If so, was the color-visual defect one of those now known to be ordinarily X-linked? If not, then was it primary at all, or only an associate of other features which have tended to disappear from modern discussions of the pedigree? Was there, then, associated with the "color blindness" any character the nature of which favors as much, or more, some genetical explanation other than the popular attached-X hypothesis?

Cunier was a leading ophthalmologist of his time. He founded an ophthalmological dispensary in Brussels in 1840, and the Ophthalmological Institute of the province of Brabant in 1849, dying four years later at the age of only forty.

Cunier had a special interest in ophthalmic conditions that appeared to be hereditary. He was an excellent observer, and no novice at obtaining pedigree information. Apart from saying once *ses cinq soeurs* where *ses quatre soeurs* was obviously meant, and letting *au-dessus* get by him in the proof (for *au-dessous*; both words are real, but have different meanings), his account is detailed and informative, and remarkably free even of those flaws for which one expects to have to excuse any pre-Mendelian.

It was rather unfair of Döderlein (1921) to suggest that perhaps the mystery of female-to-female transmission of color blindness need not be explained at all since Cunier may only have taken information from laymen too much at face value. Döderlein seems to have thought that the proposita was in the fifth generation and that Cunier got most of his information from her, for the reason he gives for deeming the information necessarily unreliable is that to go back five generations from 1838 would carry one into the seventeenth century. This displays some bad arithmetic as well as ignorance of what is actually in Cunier's paper.

Cunier's account does leave some important points uncertain, some important questions unanswered. His information about I-1, II-2, II-3, and IV-8 was certainly second-hand (obtained from III-3 and IV-1), since these females were all dead before his first contact with the family (via III-3), as were also the males II-1 and III-1. Moreover it is not clear how many of the fourteen other decisive individuals in the pedigree were actually seen by Cunier. One readily gets the impression that he examined all of them, from such a passage as this: "*. . . l'inspection attentive des yeux des filles et petites-filles de* [III-3] *n'offre rien de particulier; elle et ses six enfants ont l'iris gris-brun. Il en est de même de toutes ses petites-filles. L'iris des garçons est noir chez trois, et de coloration bleues plus ou moins foncée chez les autres.*" But IV-8 had been dead four years when Cunier came along, and if he ever met IV-10 and actually found him to have gray-brown irides like his mother, his sisters, and his nieces, this would rather have spoiled the tie between this iris coloration and the color-visual defect which Cunier was at pains to establish elsewhere in his paper. Since we know Cunier did not see all of the children of III-3, can we be sure he saw all of her granddaughters? Even if he did, were the children in generation V all old enough to give

reliable responses when their color vision was checked, whether by Cunier, a mother, or an aunt? We are told the ages of only two of them. V-7 was eleven, and the older of the daughters of IV-1 was eight years old.

From his remarks about the "*parties profondes*" of the eyes, it is certain that Cunier himself studied III-3, IV-1 and at least one, probably two, perhaps all three of her surviving sisters, and both daughters of IV-1. He may or may not have seen other persons. Yet, it must be said that Cunier gives a strong impression that he and his informants were certain of their facts. Along with his assessment of V-7 as color normal, he carefully mentions that the boy's father, a distinguished painter, had long feared that the boy *did* share his mother's abnormality. When Cunier was not sure himself of the reliability of second-hand information, he says so: he withheld judgment as to whether I-2 and her (unstated number of) sisters exhibited the familial color defect, for III-3 only *believed she could affirm* that they did not. Nevertheless, it is well known how deceptive memory can be and how easily errors may enter into reports about relatives distant in space or time. While the pedigree as presented here (exhibiting as usual only the "color blindness" which has received so much attention) has a high probability of being accurate, it falls short of reasonable certainty

Even if it be granted that all females and no males descending from I-1 were affected, the evidence is insufficient for a demonstration that none of these males had the genotype which was making their female relatives color-defective. Gates (1923) pointed out that none of the males had any offspring up to 1839. II-1 (and perhaps IV-10) had never married. III-1 died without issue at 62. The youngsters of generation V may have had children eventually, but history does not record them. This leaves the possibility that one or more of the eight males actually carried the abnormal genotype, the expression of this being limited, however, to the female sex.

If the abnormal phenotype depended on an autosomal dominant gene, the most probable distribution would have given this to 5.5 of the eleven females and four of the eight males. For all eleven females to be affected deviates strikingly from expectation, but for none of the eight males to be affected is compatible with normal segregation of a gene which is sex-limited in expression.

Dismissing such possibilities for the moment, and again assuming the complete and exclusive presence of the color-visual defect in the females, a prime issue is the nature of that defect. The total number of words in Cunier's paper, that add up to a description of the defect, is really small. In such an old piece of writing, this would ordinarily mean that a modern investigator would be frustrated, quite unable to make a diagnosis from so sketchy a description. But Cunier's statements are so incisive and so positive that they leave no room for doubt. The points they make are as follows:

I-1 was much annoyed to the end of her 81 years by her inability to distinguish dark blue (*bleu foncé*) objects from red (*rouge*) ones. II-2 (who died at 70) and II-3 (who died at the birth of III-3) had this same lifelong inability. III-3 and all her daughters and grand-daughters confused dark blue with dark red (*cerise*). III-3 could identify a light blue (*bleu clair*) as a blue, but anything dark blue appeared to her to be cerise. V-3 and V-4, also, could distinguish only light blues, not dark blues, from cerise. III-3, and IV-1 and her sisters confused only *bleu foncé* with cerise, not

any other shade of blue with any other shade of red; and, they did not confuse any two colors of other hues, such as green and orange, yellow and violet, etc. Nor is anyone in the family said to have confused any chromatic color with any shade of gray.

Modern color science recognizes at least four, perhaps six, X-linked "red-green color blindnesses." Protanopia and protanomaly (short for protanomalous trichromasy) have alleles interchangeable with a normality gene, and what is called "extreme protanomaly" may have an allele of its own. Deuteranopia and deuteranomaly, perhaps also extreme deuteranomaly, are represented by another series of multiple alleles. If what we may as well call "Cunier's color blindness" was any one of these physiological entities, a point in favor of the attached-X explanation is of course established.

The other, less common kinds of congenital, hereditary color blindness include total color blindness and three "partial" types: tritanopia, tritanomaly, and tetartanopia. While typical total color blindness has been claimed by Haldane (1936) to be partially sex-linked, it excludes itself from any consideration here since the affected cannot discriminate any two colors at equal intensity. Excluded for the same reason is the very rare "atypical" total color blindness, characterized by normal or supernormal visual acuity. The best evidence is that this condition is synthesized, in compound heterozygotes or in males hemizygous for either protanopia or deuteranopia and also homozygous for tritanopia (Walls and Mathews, 1952; Walls, 1955; Crone, 1956).

The gene for tritanopia is certainly autosomal, and is irregularly dominant or incompletely recessive. In the heterozygous condition it may be responsible for full-blown tritanopia, for "mild blue-yellow defects", or for something in between *called* "tritanomaly"—although the first of the few *genuine* tritanomals ever described were in a pedigree clearly indicating X-linkage: they were two brothers and their sister's son (Hartung, 1926). The status of tetartanopia, no two unquestionable cases of which have ever occurred in sibs, or in separate generations in one family, is uncertain. It may be another heterozygous manifestation of tritanopia (Walls, 1955).

Cunier himself was confident of the nature of the defect confronting him, and thought it to be a "regular" one, common outside of the family he was dealing with. It is important to note, however, that Cunier had never seen a case of any kind of "idiopathic" color blindness before—he had observed only acquired disturbances of color vision, as symptoms of developing blindness and cataract (see Appendix A). He can be forgiven for diagnosing the color defect in the females of five generations as *Akyanoblepsie.*

This name had been given by Goethe, in 1798, to a kind of partial color blindness which he believed to be common although he had only two cases of it (and did not even mention whether they were related). A supposedly distinct entity, acyanoblepsia hung on in textbooks and medical encyclopedias until a few years after Cunier's time. Any modern investigator should be able to tell that if Goethe's subjects were not protanopes, then they were deuteranopes (although they have even been interpreted as tritanopes). When "carmine" (probably, unlaked cochineal) was

painted thinly on a white saucer to make a pink spot, they called this blue and likened it to the sky. Rose-color, blue, and violet differed for them only in lightness and saturation, not in hue.

Now "rose-color" was Goethe's idea of a light, pure red, whereas to the modern mind there is some blueness in "rose." Moreover a true pink is not a pure red diluted with whiteness, but a desaturated strongly-red purple. Goethe's "acyanobleptics" could match pink and rose to lighter and darker blues, but this was because they perceived blueness (and no other hue) in all of them. Cunier's subjects identified no sort of red, with or without blueness in it, as a blue—rather, they identified deep blues as reds or deep reds. Cunier emphasized that the females of his first two generations matched dark blue to *rouge* while those of the three later generations matched dark blue to a darker red (*cerise*). He thought the difference real, and perhaps it was. If so, it would not be unexpected if the earlier women got their family reputations for their particular confusions at early ages, the women seen by Cunier being older when seen. An older person's crystalline lens absorbs so much shortwave light that she (or he) would require a darker red for a *tonal* match against a dark blue sample. The same blue, being less darkened by the lens of a younger person, would give a lightness match with a less dark red.

Much more serious than the fact that Goethe's subjects did not match the same sort of red to the same sort of blue as Cunier's, is the fact that they did match colors whose hues were neither red nor blue—green with orange, for example. Cunier had to overlook this, in order to think that he was dealing with Goethe's "discovery." He did not necessarily know of any full description of *Akyanoblepsie*, however. Cunier did not refer to Goethe, but he did list Purkinje among his authorities. Purkinje (1828) gave no full list of confusion-pairs of colors, characterizing the condition as primarily an inability to have a blueness sensation.

Whatever acyanoblepsia may have been, Cunier's people did not have it. The same confusibility of only blue and red that makes this certain, also keeps Cunier's color blindness from being identified with any other hereditary color defect for which we have a name or have ever had a name.

The Cunier defect was not total color blindness. It was not tritanopia and not tritanomaly, for these people will confuse blues with greens but never with reds, and moreover will confuse many other pairs of colors, and colors with grays. It was not tetartanopia. A tetartanope might match a red to a violet, but not to a blue. He might match a blue (or a yellow) to a gray, but never to a red.

Mere considerations of probability would say that the Cunier defect was most likely the commonest of all defects. This is deuteranomaly, whose victims outnumber all other color-blinds put together. Cunier's color blindness was not deuteranomaly. The main feature of this condition is a depression of saturation. A deuteranomal may confuse a dark blue with a dark red, but then he may confuse a dark shade of any hue with a dark shade of any other hue, or a light tint of any hue with a light tint of any other hue. He sees all such stimuli as grays if they confuse him, and this is why they confuse him. Protanomaly eliminates itself because its main feature is also a depression of saturation, with the further complication that longwave stimuli are perceived with depressed intensity, rendering many a red object apparently black.

Cunier's color blindness was not deuteranopia. A deuteranope can be confused by yellow and orange, by yellow-green and red, by green and olive and brown and pink and red-purple, by greenish-blue and gray and red-purple, by blue-green, weak blue, and purple, and by blue and violet. He will never be confused by good blue and red stimuli, since their dominant wavelengths are on opposite sides of his neutral point and they respectively give him the two hues he sees in the whole world—the normal's blue and the normal's yellow.

Only protanopia remains, not only of the known X-linked defects but of all color defects known or suspected to be X-linked or partially X-linked, or known or believed to be autosomal. But, it is little more likely that Cunier's color blindness was protanopia than that it was anything else we know of. Even so, it is the only possibility with any strength at all, just because a protanope *can* confuse a strong red with a (sufficiently dark) blue. On the average, protanopes see red lights as even dimmer than they look to protanomals; and if they see them at all, they do not experience the normal's red sensation from them, but probably a saturated green. Any object that is dark red for the normal is just very dark for the protanope. An old-time protanopic bookkeeper could distinguish his red and black inks only by reading the labels on the bottles, and his playful office mates usually took advantage of this.

Any protanope will confuse many other colors too. He can match a green to a red-orange, a blue to a purple; he confuses light blue-green, light gray, and pink, and mixes up dark green, brown, and strong red. Cunier's I-1, if she had been a protanope, would have been most exasperated by her inability to distinguish many reds from many greens, and just as perturbed over her confusion of light and medium blue with lavender and purple, as by any mixing up of dark blue and dark red.

The fact that Cunier's color blindness was not of any known, named type might seem to demand the abandonment of the attached-X hypothesis. Figure 1 is still there, though, looking more like an attached-X pedigree than anything else. The color defect may not have been X-genal, but it could still be X-chromosomal if X-attachment *per se* caused it after the fashion of a position effect.

While no position effect in attached-X chromosomes in *Drosophila* has turned up, such a finding would not have been surprising. In an ordinary X-chromosome, nearly all of the genes comprise the distalmost (and somewhat major) portion of the long arm. In attached-X complexes another long-arm gene-string is present, the short arms may or may not be present, and in any case the topographic arrangement of segments has been so altered that the occurrence of position effects is certainly rendered possible.

If human X-chromosomes do ever become attached, the possibility of position effects can hardly be denied. The expression of some gene in one of the regular (protanoid, deuteranoid) color-blindness series, or of a gene at some other, unknown locus might have been altered into Cunier's color blindness by such a position effect.

(Reed, Cambier, and Applen (1951) identified a gene, as being in the differential segment of the Y-chromosome, which in Cambier's own family causes a color defect that shows up in pseudoisochromatic-chart tests. They assumed the two-locus theory for protanopia and deuteranopia, pointed to Haldane's (1936) claim that typical achromasy is partially sex-linked, and rejected the idea that their Y gene might have

been a protanoid or deuteranoid one derived from an X-chromosome, since the gene would have had to turn dominant (which indeed might happen, as a "reversed Dubinin effect"; Stern and Heidenthal, 1944). The Y gene being concluded to have arisen by mutation within the Y, this gave them four color-vision loci in the two sex chromosomes. They thought this more than a coincidence, which in turn would make it plausible that the sex-chromosomal material has a fairly widespread potentiality for mutations (in the broadest sense) that will affect color vision. The high concentration in the X-chromosome of genes having variously to do with responsivity to radiant energy is well known. Reed *et al.* thought that no kind of color blindness is autosomal, whereas typical achromasy and tritanopia almost certainly are. On the other hand they could have counted a possible total of five sex-chromosomal loci, had they had knowledge of tritanomaly (*v.s.*).)

The underlying physiology of the Cunier defect is so baffling that it is hard to say whether it is a little, or a lot, to expect from one gene, one position effect, or one cytoplasmic factor. If one takes a free hand in rearranging hypothetical receptorocortical pathways, invoking inhibitions and facilitations and various other resorts of the theoretical neurophysiologists, one can devise an *ad hoc* scheme to account for blue and red stimuli (and no other pairs) looking alike to the individual. It would be a Great Pyramid of hypotheses.

Unprofitable though it obviously is, to explain the Cunier pedigree as one of color blindness, that is just what even the most recent treatments still do, both in textbooks and in journals—they overlook the other things that were peculiar about the eyes of Cunier's females and were not shared by their male relatives.

Only a few ophthalmologists are much interested in color blindness, since it cannot be treated and cured. Only such a rare ophthalmologist would be impelled to look for Cunier's paper by anything he might have read in his own library. But, choose an amenable ophthalmologist at random and push the paper under his nose without comment, and we venture to say that he will not be so much impressed by the "color blindness" described there, as by the peculiar appearance of the pupil noted by Cunier in several of the females (and in none of the males).

The pupil exhibited normal motor activity, but did not have the ordinary black coloration throughout its area. It contained an oval spot, yellowish except at the center, where it was green and was flattened or depressed. This was best seen in IV-1, in the older of her daughters, and in her sisters (all?). Cunier attributed this to a defect in the fundus of the eye, obviously localizing it there by projection along the line of sight that showed it up. In 1839, however, the invention of the ophthalmoscope was still a dozen years away, and without post-mortem examination ophthalmologists could only guess (often wrongly) what was retinal or choroidal, and what really stood far forward from the fundus. The localized spot in the pupil could only have been some small defect of the lens—by definition, a congenital "cataract." It must have been polar or parapolar, and was almost certainly anterior and quite likely capsular. The coloration described could readily have been produced by interference, in microscopic lamellae which had become slightly and variously separated, after the fashion of the colors in an oil film on water.

For this defect to have been certainly hereditary, it is enough that it occurred in two successive generations. It need not have occurred in *all* the sisters of IV-1. It may be important to note that most known genes for various forms of cataract are dominant (Sorsby, 1951); and, their expression is notoriously variable.

Another characteristic common in, and presumably restricted to, Cunier's females was clearly related to the cataract, although Cunier did not see the connection since he had not diagnosed the cataract. This was a pseudophotophobia, very marked in "*les enfants*" (*i.e.*, generation V; males too?). Cunier's little girls "fled the sun" because in bright light their vision was blurred. Caught unawares in a sunbeam, they would sometimes actually cry out—surely not from pain (which is not mentioned at all), but in annoyance. When the human pupil is well opened, a small anterior cataract has no more effect upon imagery than does a speck or a bubble in a camera lens; but when the pupil reflexly constricts in bright illuminations, the lens defect may then easily occupy such a percentage of its area that visual acuity is greatly deteriorated.

This pseudophotophobia had been strongest in III-3 and her daughters when they were little girls, but they told Cunier that it had greatly changed apparently beginning at puberty, and was vestigial in adulthood, although they thought it was often revivified at the approach of menstruation. The blurring of imagery in intense light may not actually have lessened at all. It, and the necessity of avoiding direct sunshine, may only have become less bothersome to the women as they grew up. For them to be more annoyed by these things (among others) during the few days before menstruation is only to be expected.

Cunier's contemporaries believed that color blindness is much more common in blonds than in brunets (although what feeble correlation there is, in England at least, is with *dark* hair and eyes; Burt, 1946). When therefore Cunier noted that the females in his material had darker hair than the males, he had a strong incentive for getting accurate information about the coloration of every available member of the family. He was able to say that in III-3, in her children, and in V-3, V-4, and V-6 the irides were gray-brown and the hair was black. The iris color was apparently darker in all the boys of generation V, for it was black in three and "more or less dark blue" in the other two (see the original French, above). For Cunier, hair color alone seems to have determined blondness versus brunetness. He disregarded the fact that the females had the lighter irides. The implication is strong that the boys all had light hair, or at least hair lighter than black; for the *whole* situation led Cunier to question sharply the supposed rarity of color blindness among dark-haired persons, as well as among females in general. What seemed so important to Cunier may have no importance now; but if III-3 and all her female descendants, and not one of her male descendants, had a very particular iris color—gray-brown—that *is* important.

If the Cunier pedigree be re-evaluated as essentially a pedigree of a unique, mild, congenital cataract, and the associated color-visual peculiarity takes the subsidiary position it probably deserves, then at least one rival of the attached-X hypothesis gains strength. If a dominant mutation showing first in I-1 was responsible for the cataract, it could as well have been responsible for a syndrome of cataract, gray-brown iris, and red-blue confusion. It may mean something that the lens and its capsule

are ectodermal, that the substrate of any color-visual defect is necessarily ectodermal, and that not only are the pigmented iris-epithelial cells ectodermal, but also (a little unexpectedly) the pigment cells in the iris stroma which are required if the color of an iris is to be anything but baby-blue.

We are by no means the first to suggest that Cunier's color blindness was actually a minor disturbance secondary to some other pathological condition of the eye—never, however, spelled out so fully as here. This brings the Cunier story full circle, for Cunier himself viewed all the exclusive features of his females as comprising a syndrome, with "absence of choroidal pigment"—partial ocular albinism—as its centrum. Since nystagmus, head-nodding, etc., were lacking, the diagnosis was naïve, but it still leaves Cunier in a better light than the many writers who have completely ignored his basis for it, seeing only "red-green color blindness" in a pure state where it did not even exist at all. We believe that the syndrome view strengthens considerably the neglected suggestion that a dominant mutation was involved.

Pleiotropic action of a sex-linked autosomal dominant seems at least as likely an explanation of the ocular status of Cunier's females and its inheritance, as does a hypothetical attachment of X-chromosomes which rendered double a known or unknown gene, or produced the syndrome as a position effect. Haldane's (1932) suggestion of an extranuclear agent, transmitted by all females and limited in expression to them, looks better than ever. Since Haldane wrote, an easily adaptable mechanism has been found. In *Drosophila bifasciata*, certain strains possess an extranuclear component which is inherited harmlessly by all females but kills most or all male embryos (Magni, 1952; Moriwaki and Kitagawa, 1954). If such a component was acquired by Cunier's kindred, one would have only to assume that it changed the phenotype in the females, but not in the males (or perhaps did not even replicate itself there).

Hypotheses still unborn will probably reawaken interest in the Cunier pedigree, perhaps again and again. Among those offered in explanation of it to date, none can be given any strong preference. In view of the great cytological difficulties in the way of spontaneous attachment of X-chromosomes in the "wild" human population, we are inclined to feel that the favorite attached-X hypothesis is not the strongest explanation of the Cunier pedigree, but perhaps the weakest.

SUMMARY

Careful examination of Florent Cunier's own account, of "color blindness" manifested by all females and only females in five generations, raises some small doubt as to the acceptability of the pedigree data. More important, it becomes apparent that the defect of color vision was slight although it may have had a very complex physiological basis, that it was not one of the typically X-linked color blindnesses nor any known autosomal type, and that it was a part of a lost syndrome in which the central element was a mild form of congenital cataract. For this and also for cytological reasons, the hypothesis that there were attached X-chromosomes in the Cunier kindred is greatly weakened, and certain other possibilities become at least as strong.

APPENDIX A

Bibliographically, the whole matter of the Cunier "color blindness" pedigree is very confusing. The original paper was entitled *Observation curieuse d'une achromatopsie héréditaire depuis cinq générations*, but in reference lists the first three words may be omitted, the first two words may be pluralized, etc. The journal is almost always abbreviated *Ann. d'Ocul.*, but may be spelled out *Annales d'Oculistes, Annales d'Oculistiques*, or (correctly) *Annales d'Oculistique.* Either 1838 or 1839 may be given as the date, or even both—one at the beginning and the other at the end of the citation. The page numbers 417, 418, 417–420, 417 *and* 488, 285, 285–288 all occur combined with various dates, title-wordings, and journal names. The only perfect agreement is upon the volume number—1.

It was impossible for us to tell which authors had read the original paper and which had not; so, we could not tell whose second-hand accounts to believe. The *Annales d'Oculistique* was founded by Cunier in Belgium, eventually moved to France, and is still the leading French ophthalmological serial. The *Union List of Serials* gave fifteen American libraries as owning vol. 1, which was lacking in the set available to us at the Stanford-Lane Medical Library in San Francisco. We sent for it through our interlibrary borrowing service, not anticipating that we would find all that we did in Cunier's paper, but at least expecting to be able to write a citation which would, of course, be absolutely correct.

That citation read:

Cunier, F. (1838) Observation curieuse d'une achromatopsie héréditaire depuis cinq générations. Ann. d'Ocul., 1, 285–288.

We could not imagine why others had given such page numbers as "417" or "417–420," or how the idea could have arisen that the paper was in two parts beginning on p. 417 and p. 488. The volume before us had only 312 pages of text, and at the bottom of p. 312 "FIN DU PREMIER VOLUME" was printed as clear as could be. We had the article copied by Contoura and sent the volume back, prematurely as it turned out.

When we examined the dependable monograph of Julia Bell (1926) for her attitude toward the Cunier pedigree, we were surprised to find that *her* reference was to a journal with the highly improbable name of *Annales d'Oculistique et de Gynécologie.* Her title for the paper with its uniquely pluralized words, her date (1839), and her pagination (417–420) all disagreed with ours. The *Union List* told us that there really was such a journal and that three American libraries own it. Apparently Cunier had written up his hologynic pedigree for two different journals. If one version was a year later than the other it might be different in important ways, and we certainly should see it; so we sent for "A.d'O.G.,1."

Reëxamination of our notes showed that all writers since Bell, even those surely familiar with her monograph, have given "A.d'O." and usually "p. 417," or 417–420 (as she has it). This made it appear that no-one has believed his eyes when he found gynecology coupled with ophthalmology in her reference to Cunier. Schiötz (1922) did cite A.d'O.G., but no-one else that we could find, besides Bell.

Volume 1 of *Annales d'Oculistique et de Gynécologie* had Cunier's main paper in

columns 417–420 (two columns per page), in the *livraison* for June 15, 1839. In columns 488–489 there was a separate, very short article entitled *Achromatopsie héréditaire*, of which more later. The 24 issues of the volume bore dates from August 1, 1838, to September 1, 1839, and the title page was dated "1838.–1839."

The versions of Cunier's article in A.d'O.,1 and A.d'O.G.,1 were seemingly intended to be exactly alike. One word, *noire*, occurred in one printing (and clearly "belonged"), but was not in the other version. Otherwise, the similarity was actually *too* close: In the A.d'O., the paper had *cinq* in error for *quatre* and *au-dessus* for *au-dessous*, and *Purkunje* and *Mackensie* had slipped by for *Purkinje* and *Mackenzie*. These very errors occurred also in A.d'O.G., yet Cunier had presumably had a year in which to spot and correct them before the second printing. We did not like to think him so careless.

A.d'O.,1 was printed in Brussels. A.d'O.G. was founded 30 miles away in Charleroi by Cunier and a Martin Schoenfeld. In its second year Cunier and ophthalmology disappeared from this journal, and Schoenfeld continued it as a short-lived *Annales de Gynécologie et de Pédiatrique*. From the appearances, Cunier had changed his mind twice. He had started *Annales d'Oculistique* by himself in 1838. Then he had been talked into establishing with Schoenfeld an odd combination journal, to which he had contributed material already printed. His lone effort with A.d'O. was charged off. But then after only a year he and Schoenfeld had decided that A.d'O.G. had been a mistake. Cunier went on with a second, 1839, volume of A.d'O., in a preface to which he tactfully described the separation and hoped that his subscribers would be pleased with the octavo format of A.d'O.—the *livraisons* of the unhandy quarto A.d'O.G. had been reaching them soiled and damaged in the post, and the printer of A.d'O.G. had done a generally poor job.

One would think that thereafter, with A.d'O. continuing in neat octavo from its 1838 vol. 1 on, that if Cunier had any mistake to conceal it was the ill-advised merger with Schoenfeld. In that venture, he may have had his fingers crossed from the start. In the preface that he wrote singlehandedly for A.d'O.G.,1, dated strangely early we thought (July 31, 1838—with A.d'O. only then about to be launched), he mentioned the new journal only under the simple title *Annales d'Oculistique*. The word *gynécologie* was set in somewhat subsidiary type on the title page as if it were meant to have the status of a subtitle, and sentences in the preface implied that gynecology's place in the journal might be only temporary, with other struggling specialties (lacking journals of their own) perhaps to be given a boost sometime by being allowed space in what would always be, fundamentally, an ophthalmological journal.

In the last sentence of his twice-published paper, Cunier spoke of how interesting it would be to see whether the little girls of his generation V would pass on their color defect to their own daughters. Cunier died "from overwork" in April, 1853. Assuming that he would have put into his own journal any new information he ever obtained about his famous family, we thought it worth while to check its contents to 1854—there might be something there which had gone overlooked. This chore was made easy by the fact that the editorial team that succeeded Cunier promptly published an index covering the 30 volumes of the 1838–1853 period. Working from this, we could quickly examine every article by Cunier on any subject, and every

paper on color vision by anyone else, for any insertion by Cunier of new information about the descendants of "Mme. Th . . ."

We found Cunier and color blindness coupled in any "new" way, up to his death, only in some confused statements by d'Hombres-Firmas (1849, 1850). In one place he said that "Withloch" and a female described by Cunier saw, as red in artificial light, curtains which looked blue to them in daylight. In another place, only "Whitloch" was said to have seen thus, while Cunier was said to have described a female for whom blues, as seen by day, became red in artificial light.

d'Hombres-Firmas was mis-spelling, in two different ways, the given name of Nicholl (1816, 1818). Whitlock Nicholl, himself *color-normal*, had three color-blind relatives—two men who were brothers, and the 11-year-old grandson of one of them. All were apparently deuteranopes. The boy's mother told Nicholl that "he called the crimson moreen curtains of his bed red by candle-light, but when he gets up he says that they are dark blue." Nicholl's second (1818) paper described another deuteranopia family in which the affecteds were a man, one of his brothers (almost certainly), and one of his nieces (possibly). The propositus told Nicholl: "I have red crimson curtains on the window of my bed-room, which appear to me red in candle-light, and blue in day-light."

The errors here are several, and d'Hombres-Firmas was probably only trying to say, in two different erroneous ways, that Cunier had once described a female to whom dark blues appeared red. By way of the curtains and candle-light, he got Cunier's female(s) mixed up with Nicholl, whom, in turn, he confused with the color-blinds Nicholl was describing. He mistook Nicholl's forename for his surname, and mis-spelled it two ways.

Cunier had learned something from Nicholl's pedigrees himself (see below). If in 1849 and 1850 he was too busy to notice (as editor) what a mess d'Hombres-Firmas had created, he naturally would not have corrected the allusion to his own (1839) color-defective females. We see no reason to think, from what d'Hombres-Firmas said (he was 74 years old at the time), that Cunier ever did describe any color-defective female outside of the family of "Mme. Th. . ."

While Cunier's journal, up to his death, contained no news of a generation VI, it did present a new puzzle. Throughout the *Tables Générales* for vols. 1–30, all items in vol. 1 were cited with paginations pertaining to A.d'O.G.,1 but not to A.d'O.,1. Going back to the first volume published after the split with Schoenfeld (*i.e.*, A.d'O.,2) we found that on the very same page (27) the titles of *both* journals occurred in foot-note references in a paper which Cunier, of course, had edited. Apparently Cunier had had trouble making up his mind whether to consider the 1838 Brussels volume, or the 1838–9 Charleroi, to be "volume one" of A.d'O.

Indeed, nowhere in the next few volumes was there a citation of an article in vol. 1 that did not give page numbers belonging only to vol. 1 of A.d'O.G. Both Cunier and his editorial successors seemed to be covering up the original 1838 octavo vol. 1 of A.d'O., *not* the big mistake of Cunier and Schoenfeld.

Much bewildered, we looked for a possible write-up of the history of *Annales d'Oculistique* in its own later volumes. There were two, one by the editor (E. Warlomont) in the 50th anniversary volume in 1889, and one by A. Rochon-Duvigneaud

who was editor when the centenary volume was issued in 1938. Warlomont showed no indication that he even knew that an 1838 Brussels, vol. 1 of A.d'O. had ever existed: he complained of how dearly he had had to pay for his own two copies of the quarto A.d'O.G.,1, inasmuch as this was so rare as to be a collectors' item. Rochon-Duvigneaud reproduced the title page and several other pages from the octavo A.d'O.,1, but said not a word about the volume in his text. The peculiar beginnings of the *Annales d'Oculistique* seemed to have become forgotten.

Came then to us the dawn. It must be that the "1838" vol. 1 printed in Brussels had not been Cunier's first venture at all, but had actually been produced long after his death and predated—printed, perhaps, even later than 1889. If the list of subscribers had become large and A.d'O.G.,1 rare, it would have been a nice gesture to reissue it, taking opportunity to change the size to octavo and to leave out everything gynecological, yielding a synthetic "vol. 1" uniform with the rest of A.d'O. This would explain why, in his color-blindness paper, Cunier had not corrected his four little mistakes between printings. And, the "1838" compositor could not have recognized any one of them *as* an error.

We needed to compare A.d'O.,1 and A.d'O.G.,1 directly, so we re-ordered both as interlibrary loans. We circularized all the libraries the *Union List* gave as owning A.d'O.,1, in the hope that accession dates, differences in binding, and so on would set this volume off and show it to have been a belated and altered reprint. We wrote to the present editor, A. Magitot, to ask what he knew about the matter. Several librarians replied helpfully, and we learned that on p. 6 of vol. 51 (1864) there was an announcement of the special printing and a promise of early distribution. Dr. Magitot, however, could give us no information relative to the production or distribution of the reissue.

The Boston Medical Library and the University of Rochester both found, when they looked for their A.d'O.,1, that it was really A.d'O.G.,1 So, not three but four American libraries own this rare volume: Boston Medical, National Medical, John Crerar, and Rochester. On the other hand Boston and Rochester, which innocently reported the book to the Union List as vol. 1 of *Annales d'Oculistique*, do not own the synthetic "1838" book. More than a dozen libraries do have it, however.

Once the two vol. 1's were in our hands together, many things became clear. The reissue must have been produced in 1864 as promised. Its printer and that of the two 1864 volumes of the journal was the same man; but in the following year, although he was still in Brussels, he no longer had his own shop. The chronologically first octavo volume of A.d'O., vol. 2 (1839), had been printed in Namur. Its title page was imitated, in the "1838" reissue, as closely as was possible considering the separation of the two print-shops by 35 miles and 25 years. Distribution must have been prompt, for the National Library of Medicine was able to tell us that its copy was acquired sometime prior to 1868.

The announcement of the reissue, in vol. 51, said that it was a reprint of the original vol. 1 (A.d'O.G.) in its entirety. The "1838" volume was no such thing. Everything that could have betrayed the initial association with gynecology was omitted, or was intended to be. On top of this the last two *livraisons* of A.d'O.G. were not repre-

sented at all, although they contained six ophthalmological articles and only three gynecological ones. This important omission kept Cunier's *second*, short paper entitled *Achromatopsie héréditaire* out of the "1838" volume, for it was in the 24th and last *livraison* of A.d'O.G. That *livraison* also contained two separate and excellent indices for the ophthalmological and gynecological contents of the whole volume. The index of the "1838" volume is utterly different from, and much inferior to, its A.d'O.G. counterpart.

These things lead us to conclude that what was turned over to the compositor of the reissue, for him to work from, was a pile of unbound *livraisons* of A.d'O.G.,1, believed to be complete but lacking the last two. The issue preceding them was a double one, which might have made it look as though it wound up the volume. For the last two issues to be lacking is not too surprising. In the first year of a journal's life, early issues are likely to be overrun, through optimism. Years later, they are numerous enough to be easy to collect. After the subscription list has shaken down, the final issues of the volume will be printed in just-sufficient numbers, and later on they will be relatively scarce.

In the 1839 vol. 2, although there are no *livraison* title pages, it is easy enough to tell that the volume was mailed out in nine parts. In the "1838" volume no attempt was made to create the appearance of separate issues. The beginnings and ends of articles do not coincide with signature breaks. The reissue was not sent out piecemeal to subscribers, accompanying their issues of vols. 51 and 52. It must have been put out as a unit, in a paper cover. There are eight blank pages scattered through the reissue, only one of which is possibly the last page of a signature. They were left blank, we found, just so as to have the most important of the department headings, "*Travaux Originaux*", fall always on a right-hand page.

When A.d'O.G.,1 and "A.d'O., 1" are directly compared, much internal evidence can be seen in the latter that its organization was left almost entirely to the judgment of a compositor. Neither the 1864 editor-in-chief (Warlomont) nor any scholarly person ever went through the incomplete A.d'O.G. volume available, to mark it detailedly for the printer. Otherwise, certain illogicalities would surely not have resulted.

Conveniently for its two kinds of readers, the A.d'O.G. had all its ophthalmological articles serially numbered in roman, its gynecological ones in arabic. There was no point to any numbering in the reissue. The roman numbers were therefore left out—except for four articles, on which the compositor absent-mindedly set them in. Encountering one of these meaningless numbers, an uninformed reader could be puzzled. The original numbering was confusing enough anyway. In A.d'O G., "XXXI" was used twice. One item, on blindness following post-abortion hemorrhage, was just as much ophthalmological as gynecological. Someone tossed a coin and it received a roman number. (Rochon-Duvigneaud [1938] missed this one, when he quipped that what no doubt brought gynecology and ophthalmology into association [in A.d'O.G.] was the gonococcus!).

The editor's preface of the reissue has less than half the wordage of the preface in A.d'O.G., yet it is firmly signed with Cunier's name, eleven years after his death.

Technically however it is not a forgery, for it is in Cunier's exact words as far as it goes—it simply comes to an end a paragraph or so before the A.d'O.G. preface begins to talk about gynecology and Schoenfeld.

On p. 219 of the "1838" reissue, the reader is reminded that when *Ann. d'Ocul.* was founded, a prize contest was announced for the best ophthalmological manuscript submitted by a certain date. All mention of a prize also for a gynecological manuscript was weeded out, but this was a half-measure. Later in both A.d'O.G. and A.d'O. it is announced that "*sept mémoires*" have been received as contest entries. In A.d'O. only four are described. The other three, being gynecological, were not listed—but *sept* did not get changed to *quatre*. The innocent reader of the "1838" A.d'O. will find no announcement of the contest early in the volume, for it was in the omitted portion of the A.d'O.G. preface. Nor will he learn which ophthalmological paper won the prize, for that information was in the "lost" 23rd *livraison* of A.d'O.G.

In columns 120 and 140 of A.d'O.G. there are lists of errata and corrigenda applying to earlier parts of the text. The "1838" compositor fixed some of these flaws but not all. Evidently he took care of each one that was obvious to him, as he came to it, and overlooked the lists when he came to those. So, bad punctuations got altered; but missing words did not get inserted.

As a job of printing, the "1838" reissue was much better than the original A.d'O.G., 1 (which Cunier had apologized for, in A.d'O.,2's preface). The few ophthalmological illustrations did suffer when they were re-engraved with the reduction necessary to fit the smaller octavo page, but the letterpress was highly superior, as was the presswork. In the one reprinted article upon which we concentrated—Cunier's—a character-by-character comparison revealed no less than 30 differences between the two printings. Only two of these were new slips introduced by the 1864 compositor: *officieur* for *officier* and *coloration ordinaire* for *coloration noire ordinaire*. The other 28 were on the other side of the balance, being improvements of punctuation and spelling and deletions of extraneous words by the "1838" compositor (which baffled us until we knew that the better job was the second printing and not the first as its false date implied).

The poor compositor, under loose supervision or none at all, could not think of everything, however. The smoothness of the patchwork, resulting from the sporadic omission of something gynecological, was not what it could have been if a competent editor had looked in on the job even in the late stage of page proofs. It was a little pitiful, for example, to have the book contain blank pages for the sake of consistency in the positioning of the important *Travaux Originaux* heading—and then to let that heading be repeated meaninglessly in the middle of a series of articles (because intervening departments, happening to contain only gynecological items, had dropped out).

How, now, should an "absolutely correct" citation of Cunier's *Observation curieuse* be drawn up? Our bibliography gives our answer.

In the index of A.d'O.G.,1 the third entry reads thus:

Achromatopsie héréditaire depuis 5 générations.— 417
id. id. 488

and in the 1854 *Tables Générales*, the grand index to vols. 1–30 of *Ann. d'Ocul.*, a

sub-entry under the name Cunier reads "*Observation curieuse d'achromatopsie hereditaire depuis cinq generations.* t. 1, p. 417, 489."

Perhaps these things were enough to make hasty writers couple pp. 417–420 and pp. 488–489 in their citations of Cunier's main paper. Certainly the first of them by itself could explain the whole form of the citation in the authoritative second edition (1896) of Helmholtz's *Handbuch der Physiologischen Optik.* The many nineteenth-century writers on color blindness who trusted and relied upon the bibliography of Wartmann (1849) were helped in a different way to make the same error. He cited Cunier, *Ann. d'Ocul.*, 1, 417 and 488—although a careful reader may notice that Wartmann was only pointing out two different places where Cunier had used the word *achromatopsie* in a sense that Wartmann did not like.

However it did happen, the wedding of paginations did take place and still manifests itself in the most modern of bibliographies. But the contents of cols. 488–489 in A.d'O.G. were not a "*suite et fin*" of the paper in cols. 417–420. The little paper there is not unconnected with the big paper, and it is a shame that it is missing from the more easily available "1838" vol. 1; but, it has its own title and should have its own citation in bibliographies.

The short article in cols. 488–489 is a sort of confession, a belated admission of ignorance. After publishing his paper in the preceding *livraison*, Cunier had learned of an article on defects of sight in a French translation of Samuel Cooper's *Dictionary of practical surgery* (one based probably upon the sixth London edition). Cooper had discussed two families, in each of which color-blind individuals had occurred in more than one generation. This convinced Cunier that the hereditary character, *per se*, of color blindness had already been established when he encountered Mme. Th... In retrospect, it can be seen that when Cunier said in his main paper that he had never before seen "color blindness" idiopathically, but only as a symptom of ocular disease, he was really insinuating that the cases theretofore described by others were not necessarily idiopathic. Cunier thought that *he* was establishing, for the first time, that color blindness may occur in two or more generations, that it is hereditary (by the criteria of his times).

One of the two families covered in Cooper's book is of little interest here. It was the subject of the first of two papers by Whitlock Nicholl (1816) and offered two deuteranopic brothers and an affected grandson of one of them. Nicholl himself was a color-normal member of this family.

The other description of which Cunier learned from Cooper is much more interesting because it was published much earlier. The family was that of a color-blind, J. Scott, and the paper consists largely of a letter from Scott himself to a clergyman named Whisson. Whisson was not a member of the Royal Society, but his friend Michael Lort was, and Lort got Whisson's paper into the *Philosophical Transactions* (for 1778; printed 1779).

Scott's father was color blind, which of course we know nowadays has no bearing. But Scott had a color-blind maternal uncle and a color-blind sister, and the latter had two color-blind sons and a normal daughter.

It is interesting that for a sample pedigree of X-linked color blindness, Haldane in his *Britannica* article on heredity (1953; unchanged since 1929) went all the way back to J. Scott and his relatives. Haldane changed Scott's daughter into a second

son, but this fortunately does not affect the value of the pedigree. Haldane however credited his information to Lort as author (as did Gates, leaning upon Cole, 1919, who omitted Scott's color-normal niece from *his* diagram). Bell (1926) makes J. Scott himself the author. Whisson should really be considered the author.

Scott's letter to Whisson was dated May 26, 1777, just three months after Joseph Priestley read to the Royal Society a letter describing the Harris brothers, the first color-blinds to receive any general scientific attention (see Walls, 1956). The Scott family was thus the first to be published on, in which affecteds in two or more generations brought out the hereditariness of "red-green" color blindness. It was also the first published family to exhibit a color-blind female. Scott himself, though no scientist, took inheritance for granted. Early in his letter he spoke of his defect as "a family failing"; and later, he mentioned that his only son was unmarried and his only daughter's children had died, "so how this impediment may descend from me is unknown."

Cunier was thus convinced of the heritability of idiopathic color blindness in general, by the earliest published pedigree that could have been convincing. The real importance of his separate little paper in cols. 488–489 of A.d'O.G.,1, is that he there admitted that he had not been the discoverer of the heritability, as he had thought when writing the *Observation curieuse*.

APPENDIX B

Florent Cunier's place in the history of human genetics is assured. The pedigree dealt with in the body of this paper should never disappear from the literature, although in future textbooks it may be shifted to the chapter entitled: "Defects of the lens." Cunier also, it will be recalled, pioneered on the first seven generations of the gigantic Nougaret pedigree of night-blindness, which was carried forward three more generations by Nettleship. That Cunier was versatile as well as energetic seems obvious from his frequent citation as authority for a large pedigree of sex-limited ichthyosis (Gates, 1923, 1929; Haldane, 1932, Cockayne, 1933).

By odd coincidence the Cunier ichthyosis pedigree also extended over five generations, with the affecteds (always given as being 13 in this case) all females. When Haldane (1932) piled up six pedigrees of assorted human defects as evidence for the formation of attached X-chromosomes in Man, this was one of them, and it appears in Haldane's Table I thus:

Character	No. of affected women	No. of unaffected sons	Reference
Ichthyosis	13	?	Cunier, *fide* Gates (1929)

In the text, Haldane said: " . . . and I have been unable to trace the original reference to Cunier's pedigree of ichthyosis. Colour-blindness, hæmophilia, and ichthyosis are well known as ordinary sex-linked recessives."

When Levit (1934) was preparing his critique of Haldane's paper, he searched Gates's 1929 book in vain for a proper reference to Cunier. He finally wrote to Gates, who replied that he was no longer able to tell where he had gotten his information about Cunier's ichthyotic kindred. Not everyone who might become interested in this fascinating pedigree would necessarily be led to write to Gates and find that this particular avenue would not carry him to Cunier's full treatment. Consider how

disconnectedly the pedigree is mentioned (with no references) in Cockayne's (1933) great work on inherited abnormalities of the skin:

> "In another family given by Cunier thirteen cases of ichthyosis occurred in five generations and all those affected were females, and the family recorded by Johnston and cited by Gaskoin was similar in this respect."

How many other writers may have picked up and relayed this information from Cockayne, we have no idea. Gates, at least, eventually gave up trying to recall *his* source, and in his 1946 book left out any mention of Cunier's ichthyosis kindred.

Just what had happened? Is it "too bad" that a valuable publication of Cunier's has become lost? Is Gates to be censured for ceasing, late in his series of books, to mention it at all? We think we have been able to reconstruct "the crime."

In "Gates, 1929" the following passage occurs:

> "A more recent pedigree of male-sex-linked inheritance of ichthyosis is compiled (Fig. 37) from data given by Sedgwick (1861). The condition is evidently transmitted by females to half their sons.
>
> "Orban-Vadja (1925) records a similar case of the disease, transmitted by females and appearing in males. Pick (1925) notes a case of two brothers affected, six other children healthy, the parents unrelated.
>
> "In another family, cited from Cunier, thirteen cases of ichthyosis are recorded in five generations, and all the affected individuals were females. The character must then behave as a dominant . . . "

A family "cited from Cunier"—by whom? Reading the above, Haldane naturally enough felt a bit adrift. Even if he asked Gates for further information, he found that he would simply have to take the ichthyosis pedigree on faith if he wanted to use it at all; so, he did.

What had stymied Gates, and then Haldane, and then Levit, was Gates's own insertion of the innocent little paragraph citing Orban-Vadja and Pick. If one goes back to Gates *1923* one finds that in that book the mention of Cunier's ichthyosis immediately follows the citation of "Sedgwick, 1861," since of course Orban-Vadja and Pick had yet to come along. It was from the 1923 work that we were led to hope that Sedgwick (1861) would contain a nice rotund reference to Cunier's own account of his ichthyotic family.

The situation does seem clear from what Sedgwick (1861) says. Before 1923, Gates's notes on Sedgwick must have covered the following *and then stopped short*:

> "But, as I had occasion to state with reference to the same point in ichthyosis, this apparent preference for the male sex is not due to any inaptitude in the female sex to the defect; for where it has primarily affected the latter, its sexual limitation is complete, as in the interesting case published by M. Cunier, where the defect occurred in thirteen individuals, belonging to five generations of one family, all of whom were females."

Anyone, having only this before him, could be forgiven for writing that Cunier had described a hologynic ichthyosis kindred. Gates made this slip, but in 1929 his mention of Orban-Vadja and Pick disconnected Cunier from Sedgwick, and thereafter Gates was unable to realize that he had made a slip, and how he had made it.

In Sedgwick's text, the very next words following the above excerpt commence a description of the foregoing females, who were color blind, and related to Mme. Th . . .,

and soon. In short, by not copying one more sentence into his notebook, Gates changed the old familiar hologynic "color blindness" pedigree into one of hologynic ichthyosis. Sedgwick's mistaken "thirteen," when there were only twelve affecteds, helped to make the two pedigrees appear distinct. Gates actually described "both" pedigrees on the same page of his 1923 book. Haldane proceeded to count the Cunier kindred *twice* in his little table of six attached-X pedigrees, but raised the number of affecteds in the supposedly separate color-blindness kindred to thirteen also. His evidence for human attached X's was thus weaker even than Levit (1934) made it appear. This miscount of thirteen "color blind" females may not have been Haldane's own error. The wrong number appears in several second-hand accounts of the Cunier color-blinds. It is given by Groenouw (1920), and in fact the error was made in what was probably the first published comment on Cunier's findings by another—Victor Szokalski, writing in the third volume of Cunier's own journal, *Ann. d'Ocul.*

We have to picture the poor little girls of Cunier's generation V "fleeing the sun," and sometimes putting on one blue stocking and one red one, and getting their mouths washed out with soap for what they said when they got trapped in a bright place. But happily we do not have to imagine them busily scratching themselves as they sat in the shadows. Ichthyosis was not a feature of their syndrome.

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The Blood Groups of a Japanese Population[1]

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THE PRESENT STUDY was undertaken to determine the gene frequency and inheritance of the recently described blood group factor "Diego" or Di^a in Japanese (Lewis et al, 1956a) and to see if there was any obvious linkage between this factor and other known blood group factors. Although the numbers studied are small it seemed worth while putting on record all observations in addition to those applying directly to the Diego system, for reports are lacking on the frequency of occurrence of several of the newer blood factors in Japanese.

The people in the population studied live in and around Winnipeg; they are not from any one part of Japan; most districts are included. The study is made up of Issei, Nisei and Sansei. (Born in Japan, first Canadian-born generation and second Canadian-born generation, respectively.) The Issei came to Canada after the First World War as single people and young married couples with or without children, not as whole family connections. The "unrelated" persons on whom the gene frequency estimates in this study are based are unrelated in the sense that they themselves know of no blood relationship and further that the Issei came from many provinces so that close relationship even several generations back is unlikely.

METHODS AND SERA

Until the latter part of the study, as will be discussed in the section on the ABO system, blood was collected by taking into saline a few drops of blood obtained by skin puncture. The tests on this were done within two hours of collection. The methods used for the various antigens are as follows: For A, B, M, P, S, C, C^w, D, E, e, k, Tj^a, agglutination by the capillary method of Chown and Lewis (1951) of cells suspended in saline (tests with anti-P and anti-Tj^a being performed at 6° C.); for K, one saline-reacting serum in the capillary and one indirect Coombs-reacting serum (Chown and Lewis, 1957a); for anti-Fy^a, U and Di^a (Wojanek), indirect Coombs; for N, well-slide; for c and Le^a, short albumin method (Lewis and Chown, 1957). The 3 *Cde·cdE* bloods were tested for D^u; no D^u was found. For differentiation between secretors and non-secretors saliva was obtained from the last 32 donors. The saliva samples were boiled for 10 minutes and centrifuged. The supernatant was diluted 1 in 2 and 1 in 4 with normal saline and tested for inhibition of anti-A, B and Le^a by the technique described by Race and Sanger (1954).

RESULTS

ABO System. (tables 1 and 2) The distribution neither agrees with the cumulative figures summarized by Wiener (1943) for other studies of Japanese, nor is it

Received June 3, 1957.

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TABLE 1. THE ABO SYSTEM

Group	Number	Frequency Observed	Frequency Expected	Number Expected	Gene Frequencies	
O	44	.3034	.3282	47.59	*O*	.5729
A	59	.4069	.4270	61.92	*A*	.2961
B	23	.1586	.1668	24.19	*B*	.1307
AB	19	.1311	.0774	11.22		
Total	145	1.0000	.9994	144.92		.9997

The numbers expected when the frequencies given by Wiener ('43) are used, and the χ^2 for the comparison between the so-expected and found are: *O* 44.23, χ^2 0.40; *A* 55.25, χ^2 0.25; *B* 31.61, χ^2 2.35; *AB* 13.63, χ^2 2.12; total χ^2 5.12, n = 2, *P* between .05 and .10. The deviation from expectation is not great and may be due to chance, yet we think the system worth restudy.

TABLE 2. ABO INHERITANCE

Observed Matings		Number of Children	O		A		B		AB	
No.	Class		Exp.	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.	Obs.
5	O × O	7	7	7						
17	O × A	38	15.1	19	22.9	19				
4	O × B	12	5.4	6			6.6	6		
3	O × AB	9			4.5	4	4.5	5		
7	A × A	28	4.4	2	23.6	26				
4	A × B	12	2.1	4	3.3	4	2.6	2	4.0	2
8	A × AB	19			9.5	9	3.8	3	5.7	7
1	B × B	4	0.8	0			3.2	4		
2	B × AB	9			2.0	1	4.5	4	2.5	4
51		138								

TABLE 3. THE M-N-S-s SYSTEM: M-N FREQUENCIES

Group	Number	Frequency Observed	Frequency Expected	Number Expected	Gene Frequencies	
MM	38	.2621	.2711	39.31	*M*	.5207
MN	75	.5172	.4992	72.37	*N*	.4793
NN	32	.2207	.2297	33.31		
						1.0000
	145	1.0000	1.0000	144.99		

TABLE 4. THE M-N-S-s SYSTEM: S-s FREQUENCIES

Group	Number	Frequency Observed	Gene Frequencies	
S+	24	.1655	*S*	.0865
S−	121	.8345	*s*	.9135
	145	1.0000		1.0000

internally consistent. We realized this inconsistency early in the study; we were finding too many AB's for the number of B's. For the last 32 specimens venous blood was obtained and the grouping back checked by means of the donor's serum; there were no discrepancies. We have used the capillary method of ABO grouping on thousands of routine blood specimens, each back checked, without coming across a disagreement; further in the family studies there were no disagreements between

TABLE 5. THE M-N-S-s SYSTEM: M-N-S-s FREQUENCIES

Group	Number	Frequency Observed	Frequency Expected	Number Expected	Gene Frequencies	
MMS	3	.0207	.0267	3.87	*MS*	.0263
MMs	35	.2414	.2444	35.44	*Ms*	.4944
MNS	14	.0965	.0847	12.28	*NS*	.0602
MNs	61	.4207	.4144	60.09	*Ns*	.4191
NNS	7	.0483	.0541	7.84		
NNs	25	.1724	.1757	25.48		1.0000
	145	1.0000	1.0000	145.00		

TABLE 6. M-N-S-s INHERITANCE

Observed Matings		Number of Children	MMS		MMs		MNS		MNs		NNS		NNs	
No.	Class		Exp.	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.	Obs.
1	MMS × MNs	4	1.03	0	0.97	2	1.03	2	0.97	0				
3	MMs × MMs	7			7	7								
2	MMs × MNs	5	0.74	1	1.76	3	1.85	0	0.65	1				
8	MMs × MNs	25			12.5	14			12.5	11				
6	MMs × NNs	11							11	11				
6	MNS × MNs	14	1	0	2.5	4	3.6	3	3.4	4	2.5	2	1	1
1	MNS × NNS	1						1						
10	MNs × MNs	31			7.75	3			15.5	17			7.75	11
3	MNs × NNS	6					1.60	1	1.4	1	1.6	2	1.4	2
7	MNs × NNs	25							12.5	16			12.5	9
1	NNS × NNs	5									2.67	1	2.33	4
1	NNs × NNs	4											4	4

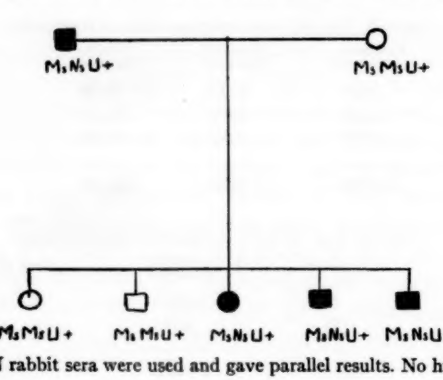

FIG. 1. Two anti-N rabbit sera were used and gave parallel results. No human anti-N was available.

the observed and the expected. It seems to us unlikely that the apparent inconsistency in results was due to technique. It may be a sampling error, or it may be that in this population there are some suppressed or extremely weak B antigens such as that described by Dunsford et al. (1956).

On rechecking some of the AB donors one was found who gave weak B reactions. similar to the reaction of A_1 cells with absorbed B anti-A serum. His serum did not contain anti-B. Further work is indicated on the ABO system. All A antigens were A_1 save one A_2 B.

MNSs System. (tables 3, 4, 5 and 6) In 1953 Wiener et al reported a new antibody that they called anti-U. In 1954 Greenwalt et al in studying such an antibody concluded that it was related to the MNSs system and that it "could most easily be thought of as anti-S + anti-s, or as anti-Ss" since it reacted with all the bloods that reacted to either anti-S or anti-s but did not react with bloods that did not react with either of these two anti-sera. We have accepted this interpretation and have tested all bloods with anti-S and anti-U; all reacted to anti-U. A blood that is shown as *ss* is therefore S-negative, U-positive by test and s-positive by interpretation, so that it is on this basis that the gene frequencies and inheritance of *S* and *s* have been determined. Family studies showed *S* to be associated more frequently with *N* than with *M*. A weakly reacting *N*, presumably a variant, was found in one family; its inheritance is shown in figure 1.

The P System. (tables 7 and 8) In 1951 Levine et al (1951) reported a new antibody they called anti-Tj^a. Sanger (1955), observing that all persons reported to have produced anti-Tj^a were P-negative, studied the relationship of this antibody to the P blood group system, and concluded that "the facts would fit . . . if the P system were constructed on the A_1A_2O pattern", anti-P being analogous to anti-A_1 and anti-Tj^a to anti-$A_1 + A_2$ $(\alpha + \alpha_1)$ in the blood of a group O person. The genes of the P system under this interpretation then become P_1 (reacting with anti-P and anti-Tj^a), P_2 (reacting with anti-Tj^a but not with anti-P) and p (reacting with neither). We have accepted this interpretation and have tested all P-negative group O bloods with anti-Tj^a (our anti-Tj^a contains anti-A + anti-B); all such were positive. If p, under Sanger's interpretation, exists in this population, its frequency

TABLE 7. THE P SYSTEM

Group	Number	Frequency Observed	Gene Frequencies	
P+	59	.4069	P_1	.2299
P−, Tj(a+)	86	.5931	P_2	.7701
	145	1.0000		1.0000

As stated in the text, there are two antibodies, anti-P and anti-Tj^a, and three antigens, P_1, P^2 and p. Anti-P reacts with antigen P_1, anti-Tj^a with antigens P_1 and P_2. The antigen p is assumed to be absent from the population.

TABLE 8. P INHERITANCE

Observed Matings		Number of Children	$P+$		$P-$	
No.	Class		Exp.	Obs.	Exp.	Obs.
14	P+ × P+	47	38.1	36	8.9	11
22	P+ × P−	58	32.8	32	25.2	26
14	P− × P−	33	0	0	33	33
50		138				

must be exceedingly low, just as it is in Whites; we have assumed its absence and estimated the frequencies of the genes P_1 and P_2.

Rh System. (table 9) The frequencies of the Rh phenotypes were as follows:—

C	c	D	E	e	No.	Percentage Frequency	Genotypes possibly included in the phenotypes
+	+	+	+	+	62	.4276	*CDe·cDE*; *Cde·cDE*; *CDe·cdE*; *CDE·cde*; *CDE·cDe*; *CdE·cDe*.
+	−	+	−		59	.4069	*CDe·CDe*; *CDe·Cde*.
−	+	+	+	−	14	.0965	*cDE·cDE*; *cDE·cdE*.
+	+	+	−		6	.0414	*CDe·cde*; *CDe·cDe*; *Cde·cDe*.
−	+	+	+	+	3	.0207	*cDE·cde*; *cDE·cDe*; *cdE·cDe*.
+	−	+	+	+	1	.0069	*CDe·CDE*; *Cde·CDE*; *CDe·CdE*.
					145	1.0000	

It is quite certain that the genes *CDe* and *cDE* are the common ones, *CDe* being much more frequent than *cDE*, in agreement with earlier studies, while the genes *Cde* and *cdE* were shown to be present by the family studies in table 9. On the other hand it was not possible to prove or disprove the presence of *cde*, *cDe*, *CDE* or *CdE*; an attempt to determine gene frequencies seemed likely to mislead. In other studies we have observed as had others (Ceppellini et al, 1955) that when *Cde* is partnered with a *D*-positive gene the reaction of *D* is frequently, though not invariably, depressed (Chown and Lewis, 1957b), while when *CDE* or *CdE* occurs in combination with *cde*, *cDe*, *cDE* or *cdE* the reaction of C to certain anti-C sera is depressed, as originally reported by Race et al. (1954). In the present study there were no such reactions which might have hinted at the genotype. None of the bloods was C^w-positive.

The Kell-Cellano System. The group of 145 unrelated were all found to be K−; 40 were tested with anti-k and found to be k+; a small number have subsequently been tested with anti-Kp^a and anti-Kp^b recently described by Allen (1956, 1957)

TABLE 9. RH INHERITANCE

Matings		Number of Children	Class of Children						
No.	Class		*CCDee*	*CcDEe*	*ccDEE*	*CcddEe*	*CCDEe*	*CcDEE*	*CcDee*
12	CCDee × CCDee	39	39						
5	CCDee × ccDEE	14		14					
2	ccDEE × ccDEE	5			5				
13	CCDee × CcDEe	43	16	24		3*			
11	CcDEe × CcDEe	24	10	11	3				
3	ccDEE × CcDEe	4		2	2				
1	CCDEe × CCDee	2	1				1		
1	CCDEe × ccDEe	2		1				1	
1	CcDEe × CcDee	2	2						
1	CCDee × CcDee	3	2						1
		138							

* The 3 CcddEe children were all in one family. One of the two other children in the family was CCDee and one CcDEe. The parents are assumed to be genotype *CDe·Cde* and *CDe·cdE*; the three children *Cde·cdE*; of the remaining two, one *CDe·Cde* and one *CDe·cdE*.

TABLE 10. THE DUFFY SYSTEM

Group	Number	Frequency Observed	Gene Frequencies	
Fy(a+)	144	.9931	Fy^a	.9169
Fy(a−)	1	.0069	Fy^b	.0831
	145	1.0000		1.0000

TABLE 11. THE DIEGO SYSTEM

Group	Number	Frequency Observed	Gene Frequencies	
Di(a+)	10	.0690	Di^a	.0351
Di(a−)	135	.9310	Di^b	.9649
	145	1.0000		1.0000

TABLE 12. DIEGO INHERITANCE

Observed Matings		Number of Children	Di(a+)		Di(a−)	
No.	Class		Exp.	Obs.	Exp.	Obs.
1	Di(a+) × Di(a+)	3	2.3	1	0.7	2
8	Di(a+) × Di(a−)	24	12.2	15	11.8	9
41	Di(a−) × Di(a−)	111	0	0	111	111
50		138				

and the presence of Kp^b established. In the 50 K− × K− matings all 138 children were found to be K−.

The Duffy System. The gene frequencies for the Duffy blood groups are set out in table 10. Of 50 matings all were Fy(a+) × Fy(a+) and all 138 children Fy(a+). In 50 unselected matings 49.31 would be expected to be Fy(a+) × Fy(a+) while among 138 offspring of such matings 137.19 would be expected to be Fy(a+). After completion of the study we identified an anti-Fy^b serum and tested 10 unrelated Fy(a+), 2 of whom were Fy(b+) and 8 Fy(b−).

This proves the presence of Fy^b in this population. We have assumed the absence of Fy(a−b−) persons in the population, such as Sanger et al (1955) have shown to occur in some Negro populations, and estimated the frequency for Fy^a and Fy^b on a two allele gene basis.

Diego System. (table 11) The antibody anti-Diego or Di^a was first referred to by Levine et al (1954). It has since been found not to react with the blood of any of 2600 Whites (Levine et al 1956; Layrisse and Arends, 1957; van Loghem 1957) but has been found to react with that of four Venezuelan Indian stocks (Layrisse and Arends, 1956a), two Brazilian tribes (Junqueira et al, 1956), Chippewa in Northern Minnesota (Lewis et al, 1956a), Japanese and Chinese (Layrisse and Arends, 1956b). It has not been found to react with pure-blood Negroes (Layrisse 1956), with Eskimos (Lewis et al, 1956b), or with Polynesians (Simmons 1957). Layrisse et al (1957) have recorded its inheritance in three Indian families in one of which it was traced through four generations; it appears to be inherited as a simple dominant. Anti-Di^b, which should react with practically 100 per cent of Whites, has not yet been identified. Witebsky (1956) found the second example of anti-Di^a in a White in Buffalo; it was identified by Levine and Robinson (1956).

Levine et al (1956) reported that "study of the antigens for Di^a, ABO, MNSs,

Rh, Kk, Fy^a, Jk^a, Le^a and P" in the family in which the factor was originally found "failed to reveal obvious linkage", and that "Di^a was serologically independent of the factors Mi^a, Ven, Ca, Be^a, Wr^a, By^a, Rm, C^w, C^x, E^w, He and V". (One of us (H.K.), who is Di(a+) is negative to the following anti-sera: Mi^a, Be^a, By^a, Kp^a, He, Lu^a, E^w, C^w). In our family studies there is no obvious linkage between Di^a and any other blood group examined. Our results are confirmatory of the earlier reports. The inheritance of Di^a in a single large sibship is set out in Fig. 2. One

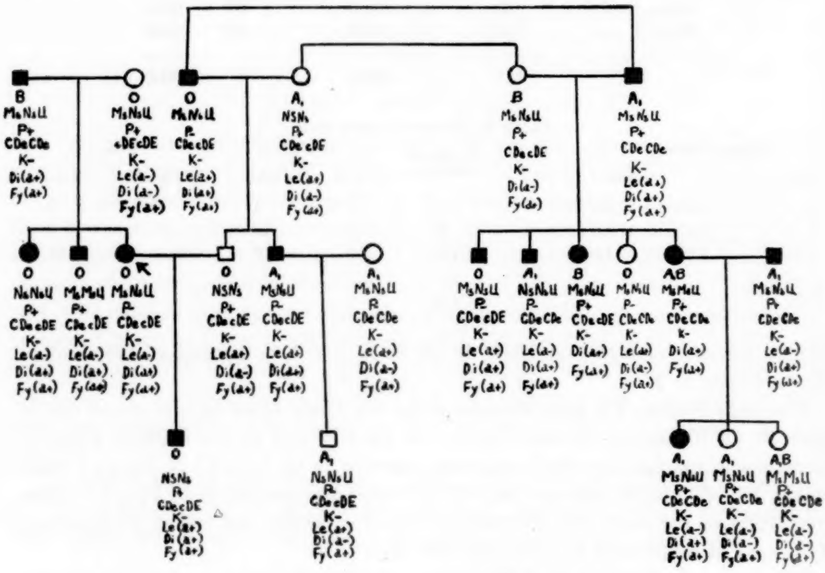

FIG. 2. Pedigree to illustrate inheritance of Di^a

TABLE 13. THE LEWIS SYSTEM

Group	Number	Frequency Observed
Le(a+)	26	.2524
Le(a−)	77	.7476
	103	1.0000

TABLE 14. LEWIS INHERITANCE

Observed Matings		Number of Children	Le(a+)		Le(a−)	
No.	Class		Exp.	Obs.	Exp.	Obs.
4	Le(a+) × Le(a+)	8	8	6	0	2
10	Le(a+) × Le(a−)	23	7.7	3	15.3	20
15	Le(a−) × Le(a−)	42	4.7	7	37.3	35
29		73				

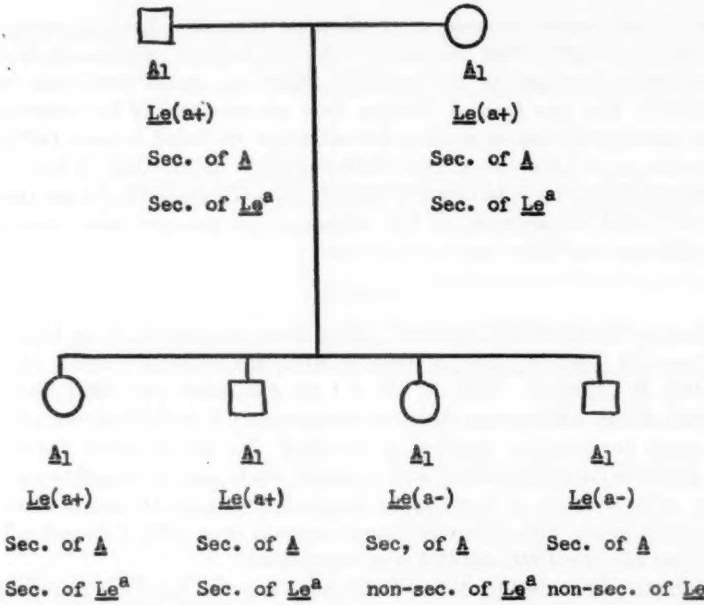

FIG. 3. Family in which secretion of *A* substance occurs in both Le(a+)and Le(a−) members. The anti-Le^a serum was one we have used for over a year. It gives a frequency in adult whites of 23%.

member of this sibship was three weeks of age when tested; his cells reacted as strongly as do adult Di(a+) cells.

The Lewis System. (tables 13 and 14) The genetic constitution of the Lewis system is still not certain. It has generally been considered that the gene Le^a is recessive, cells of adults agglutinated by anti-Le^a identifying the homozygote $Le^a \cdot Le^a$; Ceppellini however (1954) presented evidence that adult Le(a+) bloods might be either homozygous or heterozygous, while Levine et al (1955) recorded, inter alia, a mating Le(a+) × Le(a+) giving rise to one Le(a+b−) and one Le(a−b+) child.

Table 14 summarizes the Lewis matings in our study; the calculations in it were based on the concept that phenotype Le(a+) represents $Le^a \cdot Le^a$. Both the finding of two Le(a−) children in the Le(a+) × Le(a+) mating and the divergence from expectation of offspring in the mating Le(a−) × Le(a−) makes it evident that the basis of calculation must be wrong in this population; Le(a+) does not represent genotype $Le^a \cdot Le^a$ solely.

The family with the two Le(a−) children in an Le(a+) × Le(a+) mating is set out in figure 3. Both parents and all four children are secretors of A substance, which is contrary to the findings reported for Whites (Grubb '51, Andresen et al '50) and for American Negroes (Miller et al '54), secretion of ABH substance being confined in them to Le(a−) persons. We observed that all members of the family

(figure 3) were weaker secretors of A substance than were Le(a−) tested at the same time, and further that the saliva of the two Le(a−) members of the family was somewhat stronger in its inhibiting effect on anti-A than was that of the Le(a+). The two Le(a−) children were non-secretors of Le^a substance; in Whites and Negroes non-secretors of Le^a substance are found in some Le^a(a−b−) persons but not in Le(a−b+), from which one might deduce that the two children are probably Le(a−b−). In Grubb's Swedish series (Grubb 1951) 9.8 per cent were Le(a−b−) and non-secretors of Le^a substance, 7.8 per cent being secretors of ABH substance and 2 per cent non-secretors.

SUMMARY

In a study based on 145 unrelated Japanese the frequencies of the blood group genes were: M .5207, N .4793, S .0865, s .9135, MS .0263, Ms .4944, NS .0602, Ns .4191; P_1 .2299, P_2 .7702; K .00, k 1.00; Fy^a .9169, Fy^b .0831; Di^a .0351, Di^b .9649. In the ABO system there was a discrepancy between observed and found that verged on statistical significance; we think this system worth restudy in a larger Japanese population, along with a secretor study since we found two Le(a+), persons to be secretors of A substance. In the Rh system *CDe* and *cDE* were the predominant genes, with *CDe* much more common than *cDE*; *Cde* and *cdE* were present but *cde*, *cDe*, *CDE* and *CdE* were not defined.

Inheritance was studied for all the blood group systems; there was no discrepancy between expected and found.

The recently described antigen Di^a was traced through three generations of one large sibship as well as through smaller sibships. The gene is inherited as a simple Mendelian dominant. There was no obvious linkage with any other blood group system investigated.

ACKNOWLEDGEMENTS

Our thanks are due to Dr. F. J. Alcock, late Director, National Museum of Canada, for his continued support of our Canadian population studies; to Dr. Ernest Witebsky, Buffalo University, for the gift of anti-Di^a serum, and to Dr. Fred H. Allen Jr., for the gift of the Kp^a and Kp^b sera. We would express too our gratitude to our Japanese fellow-citizens for their cooperation in this study.

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Inbreeding in Brazil*

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INTRODUCTION

ALTHOUGH the genetic implications of consanguineous matings in human populations were recognized in the first years of Mendelism through the pioneering work of Garrod, it is only recently that enough data have been collected for an evaluation of the intensity of inbreeding in specific human populations. It is the purpose of the present paper to record data for a population concerning which there has previously been relatively little information.

METHOD

The method here used has been described previously (Freire-Maia, 1952). In this section, we will discuss only its validity and the magnitude of the errors involved.

Only data on Catholic marriages were used. This raises, of course, the question whether the findings can be safely extended to the whole population. The frequency of Roman Catholics in Brazil is about 93 per cent, with the lowest frequencies in the southernmost State, Rio Grande do Sul (84%), and the highest in the northern Piaui (99%). (All the census information reported in this paper has been obtained in 1950 unless otherwise specified.) Assuming random mating, we would have about 0.5 per cent of marriages between non-Catholic people, 13 per cent mixed marriages, and 86.5 per cent between Catholics. Certainly the figures vary enormously according to the relative size of the non-Catholic group in each community as well as to the degree of social pressure against mixed marriages. These tend to occur at lower rates than those prevailing in a panmictic society. It is known that the great majority of marriages between Catholics and non-Catholics are consecrated by the Roman Catholic Church due to familial and social pressures, and this is also true for marriages between non-sectarian people. For this reason, it seems reasonable to assume that non-Catholic marriages would represent probably less than 5 per cent of all Brazilian religious marriages, and that figures based only on marriages involving Catholics may with a small error be taken as representative of Brazil as a whole.

The incidence of unions not consecrated by any religious denomination varies greatly from region to region, it being a commonplace to say that it is generally higher in urban than in rural communities. The frequency of marriage records with brides

* This research was supported in part by grants from the National Research Council of Brazil and the Rockefeller Foundation. The paper has been prepared at the Department of Human Genetics of the University of Michigan, when the author was holding a fellowship from the Rockefeller Foundation.

Received February 23, 1957.

and/or grooms incapable of declaring their father's or mother's name (sometimes even both) has been shown to be much lower now than about one hundred years ago in the Archdiocese of São Paulo (Freire-Maia, 1952). Some regions in the North present a very high frequency of unmarried mothers. For instance, in the State of Maranhão, it is estimated that about 50 per cent of the unions do not have religious records. Data from the 1940 census for the same State show that about 50 per cent of the unmarried women have had living children. The frequency of unmarried mothers more than 12 years old was higher than 30 per cent in Maranhão and Pará. If, in these populations, the unmarried fraction shows frequencies of consanguineous unions very different from those found in the Catholic married fraction, a significant difference would result. Only a direct survey of the situation, with the inclusion of all couples, married and unmarried, would clarify the problem. However, we think that no great deviation is to be found between these two population fractions because it is quite common for unmarried couples to have their union consecrated by the Church after a period of common-law marriage. It is estimated that in some regions this kind of marriage may attain frequencies as high as 50 per cent.

Our data refer to urban and rural populations taken together. The proportions of each within each locality varies enormously, from almost 100 per cent urban in big cities (e.g., 95% in the City of São Paulo) to almost 100 per cent rural as in some small villages of the hinterland. There is a tendency for the predominantly rural communities to present the highest inbreeding rates, but our data unfortunately do not permit differentiating between rural and urban populations within each parish.

It ought to be mentioned also that the present data are not strictly comparable to those collected through the use of procedures, employed by a series of investigators, involving samples of all marriages in a population regardless of when they occurred. In the present method, inbreeding levels have been estimated from samples of marriages contracted in a given period. For this reason almost all the populations studied would be expected to be characterized, at the time of their analysis, by frequencies of consanguineous marriages somewhat higher than would be suggested by the estimate based on current marriages. On the basis of the data at our disposal, the majority of contemporary populations would present rates about 20 per cent higher than those detected by the method here employed.

All the frequencies will be presented as percentages. The following abbreviations and terms (some of them taken from Spuhler and Kluckhohn, 1953, and Schull, 1953) will be used in the tables with data on inbreeding.

N—Total number of marriages contracted in the given period.

UNi + ANe—Marriages between uncles and nieces plus marriages between aunts and nephews.

1C—Marriages between first cousins.

1½C—Marriages between first cousins once removed.

2C—Marriages between second Cousins.

(In our previous papers (1952, 1954), in which the Brazilian nomenclature was translated literally into English, the first cousins once removed and the second cousins were called respectively second cousins and third cousins.)

T—Total frequency of consanguineous marriages up to and including second cousins. (In the text, the expressions "total frequency of consanguineous marriages" or "total frequency" will always have the same meaning.)

Sub-Total—Total not including the state capital (indicated by ※).

α—Mean coefficient of inbreeding of the population for autosomal genes, calculated according to Haldane and Moshinsky (1939). Identical to Wright's F-coefficient (Wright, 1922, 1951).

Multiple consanguinity, relatively common in some localities, has been disregarded in the frequency data, with each marriage entered only once and marriages involving multiple degrees of consanguinity entered in the column belonging to the closest degree involved if the degrees are different. All the degrees of multiple consanguinity, however, were used for the α calculation. So, sometimes α has a value higher than would be inferred from the tabular data, and thus expresses the breeding structure of the population more accurately. Naturally, all values of α to be presented are somewhat smaller than the true ones as they do not include data on the frequencies of consanguineous marriages with degrees lower than second cousins. The difference, at least regarding second cousins once removed and third cousins, has been proved to be very small in some Brazilian populations (Freire-Maia, 1953, and unpublished data).

The values of α are generally a little lower (about 20%) than one-tenth of the frequencies of first cousin marriages. This fact provides an easy and rapid way of obtaining an approximate idea of the values of α.

Our tables will not present all the data we have collected regarding localities, but only those thought to be representative of two of the five Brazilian regions. The others, together with information on the inbreeding levels in other Latin American countries (Argentina, Puerto Rico, and Uruguay), have been presented elsewhere (Freire-Maia, 1957a).

THE DATA

Geographic distribution

National level. The distribution of the inbreeding rates in Brazil is highly heterogeneous (*cf.* table 1 and Fig. 1). The South is characterized by relatively low frequencies of consanguineous marriages, the central part of the Northeastern region presents the highest coefficients of inbreeding in the whole country, and with only a few exceptions, the other regions show intermediate situations. There is, however, a remarkable homogeneity within each socioeconomic zone (table 1, Fig. 1).

In some regions, very clear inbreeding gradients could be found. For instance, in the Northeast the intensity of the inbreeding increases from the coast to the interior (Fig. 1). One of these gradients is formed by the following inbreeding coefficients, 0.00121, 0.00176, 0.00565, 0.00830, 0.00967, involving three States, from the northern region of Alagoas to the interior of the State of Piaui. Another gradient, from the northern Bahia coast (East region) to the coast of Ceará (in the Northeast)

TABLE 1.—FREQUENCIES OF CONSANGUINEOUS MARRIAGES IN SOME BRAZILIAN DIOCESES

States and Dioceses	Period	N	UNi+ ANe	1C	1½C	2C	T	α
Rio Grande do Sul								
Porto Alegre	1946–51	4032	0.05	1.17	0.30	0.27	1.79	0.00097
Passo Fundo	1954	2404	0	0.83	0.17	0.37	1.37	0.00063
Vacaria	1954	1163	0	2.58	0.26	1.03	3.87	0.00185
Caxias do Sul	1954	2104	0	0.76	0.48	1.71	2.95	0.00091
Santa Catarina								
Florianópolis	1948–51	4361	0.02	1.17	0.53	1.83	3.55	0.00121
Lages	1954	3968	0.02	1.06	0.35	0.28	1.71	0.00089
Paraná								
Curitiba	1945–51	23615	0.02	1.23	0.55	0.99	2.79	0.00112
Palmas*	1954	2181	0.05	0.32	0.14	0.27	0.78	0.00034
Foz de Iguaçú	1954–55	4172	0	0.46	0.16	0.41	1.03	0.00044
Ponta Grossa	1951–53	7757	0.06	1.11	0.48	0.72	2.37	0.00106
Jacarèzinho	1947–49	14019	0	1.28	0.29	0.43	2.00	0.00098
São Paulo								
Santos	1944	1700†	0	0.94	0.12	0.12	1.18	0.00064
São Carlos	1954	3819	0	0.29	0.02	0.34	0.65	0.00024
São Paulo	1939–50	46465	0.01	0.78	0.19	0.23	1.21	0.00059
Botucatú	1954	3368	0	0.80	0.27	0.27	1.34	0.00066
Assis	1952–53	6918	0.03	1.68	0.49	0.42	2.62	0.00133
Bragança Paulista	1954	1415	0.57	0.71	0.21	0.21	1.70	0.00148
Jaboticabal	1954	1574	0	1.65	0.32	0.38	2.35	0.00119
Rio Preto	1954	4182	0	1.00	0.17	0.24	1.41	0.00073
Piracicaba	1954	1148	0.09	0.43	0.17	0.70	1.39	0.00064
Campinas	1951	4821	0	0.60	0.04	0.33	0.97	0.00044
Lins	1955	4334	0	0.88	0.14	0.16	1.18	0.00062
Minas Gerais								
Belo Horizonte	1951	3651	0	3.40	1.72	1.78	6.90	0.00294
Pouso Alegre	1954	3895	0.08	2.95	1.31	2.28	6.62	0.00275
Guaxupé	1953	3089	0.03	2.82	1.39	1.68	5.92	0.00250
Campanha	1951–52	7251	0.07	5.16	2.00	2.32	9.55	0.00450
Leopoldina	1954	3252	0	2.06	0.55	1.02	3.63	0.00170
Aterrado	1954–55	2483	0	6.32	1.97	3.83	12.12	0.00537
Uberaba(1)	1948–49	5646	—	3.29	1.51	—	—	0.00284‡
Arassuaí	1954	7091	0	2.88	1.03	1.20	5.11	0.00242
Rio de Janeiro (State)								
Niteroi	1954	1698	0	1.18	0.41	0.53	2.12	0.00103
Barra do Piraí	1954	1460	0.07	1.30	0.48	0.20	2.05	0.00108
Valença	1954	1272	0	1.18	0.23	0.16	1.57	0.00085
Distrito Federal								
Rio de Janeiro City								
Estácio de Sá (parish)	1946–56	1172	0.09	0.42	0.17	0.09	0.77	0.00044
Mato Grosso								
Cuiabá	1934–52	1875	0.05	2.24	0.38	0.64	3.31	0.00168
Cáceres	1953	376	0	2.66	0.27	0.79	3.72	0.00204
Ch. dos Guimarães	1952	120	0	4.17	2.50	0.83	7.50	0.00378
Corumbá	1953	2137	0.05	0.70	0.19	0.09	1.03	0.00057
Goiás								
Goiás	1937–53	3026	0	2.58	0.56	0.76	3.90	0.00191

TABLE 1.—*Concluded*

States and Dioceses	Period	N	UNi+ ANe	1C	1½C	2C	T	α
Bahia								
Salvador	1932–52	4689	0.02	2.96	0.83	0.92	4.73	0.00228
Ilhéus	1945–49	2245	0.04	2.18	0.67	1.34	4.23	0.00184
Caetetê	1954	1923	0	9.10	3.90	8.84	21.84	0.00829
Bomfim	Recent	4095	0.02	4.67	1.39	1.81	7.89	0.00400
Sergipe								
Aracajú	1954	3815	0.10	4.04	0.63	1.65	6.42	0.00315
Pernambuco								
Pesqueira	1954	3846	0.03	6.71	2.05	3.90	12.69	0.00565
Nazaré	1954	3399	0.21	1.97	1.44	2.03	5.65	0.00236
Garanhuns	1954	5103	0	2.21	0.53	1.02	3.76	0.00176
Petrolina	1950	3063	0.26	9.50	2.74	5.00	17.53	0.00830
Paraiba								
João Pessôa	1954	5537	0.09	3.79	0.41	1.81	6.10	0.00301
Rio Grande do Norte								
Caicó	1954	936	0.11	5.88	1.28	3.84	11.11	0.00499
Ceará								
Fortaleza	1953–54	14615	0.27	4.82	1.40	2.50	8.99	0.00433
Crato	1953	4217	0.40	8.42	2.80	3.91	15.53	0.00736
Piaui								
Oeiras	1954	1931	0.57	10.67	3.73	6.00	20.97	0.00967
Alagoas								
Penedo	1954	3566	0.19	6.23	1.99	3.28	11.69	0.00579
Maceió	1952	4394	0.05	1.52	0.20	0.55	2.32	0.00121
Pará								
Santarem	Recent	1318	0.91	0.30	0.61	0	1.82	0.00156
Xingú	1951–55	578	0.17	1.04	0.52	1.38	3.11	0.00124
Amazonas and Guaporé								
Porto Velho	1955	365	0.27	2.74	0	0.55	3.56	0.00214
Maranhão								
Pinheiro	1954	1423	0	0.70	0.28	1.13	2.11	0.00098

* Includes a part of the State of Santa Catarina.
† Estimate based on data of neighboring years.
‡ Assuming 2% of second cousin marriages.
(1) Previously reported in Freire-Maia (1952).

is formed by the following coefficients: 0.00228, 0.00400, 0.00830, 0.00736 and 0.00436. This gradient has its ends at zones with relatively low inbreeding rates, and so the increase is centripetal from both of them towards the diocese of Petrolina (State of Pernambuco).

Diocese level. The distribution of the inbreeding rates is somewhat heterogeneous within each diocese (tables 2 and 3). Each diocese can be defined by its mean total frequency of consanguineous marriages, or better, by its mean coefficient of inbreeding, but the values for its parishes generally fluctuate widely around the mean for the diocese.

FIG. 1. INBREEDING LEVELS IN THE BRAZILIAN TERRITORY. THE DIAMETERS OF CIRCLES ARE PROPORTIONAL TO THE VALUES OF THE INBREEDING COEFFICIENTS OF TABLE 1.

States: 1—Rio Grande do Sul; 2—Santa Catarina; 3—Paraná; 4—São Paulo; 6—Rio de Janeiro; 7—Minas Gerais; 8—Espírito Santo; 9—Bahia; 10—Sergipe; 11—Alagoas; 12—Pernambuco; 13—Paraiba; 14—Rio Grande do Norte; 15—Ceará; 16—Piaui; 17—Maranhão; 18—Pará; 19—Amazonas; 20—Goiás; 21—Mato Grosso; *Federal District:* 5—Rio de Janeiro city. *Territories:* 22—Guaporé; 23—Acre; 24—Rio Branco; 25—Amapá.

Trends in time

There is generally a tendency for decreasing inbreeding rates with time. Some examples have already been given in our paper of 1952, and others may be seen in tables 3 and 4. Sometimes the decrease is so rapid that the time gradient may be discovered in very short periods.

Sometimes no clear change is present, but only chance fluctuations leading even to small increases of the inbreeding rates. However, real "reversed" trends with

TABLE 2. FREQUENCIES OF CONSANGUINEOUS MARRIAGES IN THE STATE OF MINAS GERAIS (ARCHDIOCESE OF BELO HORIZONTE, 1951)

Localities	N	UNi + ANe	1C	1½C	2C	T	α
S. Sebastião do Curral	57	0	17.54	3.51	10.53	31.58	0.01371
Indaiá	69	0	14.49	2.90	5.80	23.19	0.01178
Camacho	56	0	8.93	14.29	3.57	26.79	0.01060
Rio do Peixe	55	0	12.73	1.82	7.27	21.82	0.00994
Pompéu	83	0	12.05	2.41	1.20	15.66	0.00847
Itaguara	45	0	6.67	6.67	13.33	26.67	0.00833
Papagaio	67	0	8.96	1.49	4.48	14.93	0.00676
Martinho Campos	111	0	6.31	5.41	4.50	16.22	0.00676
Pitangui	89	0	7.87	1.12	2.25	11.24	0.00597
Sabará	72	0	6.94	2.78	0	9.72	0.00521
Mateus Leme	94	0	3.19	4.26	6.38	13.83	0.00482
Itapecerica	105	0	3.81	2.85	2.86	9.52	0.00461
Caeté	33	0	6.06	0	0	6.06	0.00379
Sete Lagoas	180	0	5.00	1.11	1.11	7.22	0.00373
Lagoa Santa	83	0	2.41	3.62	3.61	9.64	0.00320
Pedro Leopoldo	65	0	3.08	1.54	4.61	9.23	0.00313
Baldim	104	0	3.85	0	0.96	4.81	0.00255
Santa Luzia	78	0	3.85	0	0	3.85	0.00240
Itauna	132	0	1.52	2.27	0.76	5.30	0.00225
Carmo do Cajurú	71	0	0	2.82	7.04	9.86	0.00198
Divinópolis	216	0	1.85	2.32	0	4.17	0.00195
Pará de Minas	110	0	1.82	0.91	2.73	5.46	0.00185
Betim	76	0	1.32	2.63	0	3.95	0.00164
Rio Acima	43	0	2.33	0	0	2.33	0.00145
Crucilândia	46	0	0	4.35	0	4.35	0.00136
Belo Horizonte *	1469	0	1.02	0.48	0.27	1.77	0.00083
União de Caeté	42	0	0	0	2.38	2.38	0.00037
Sub-total	2182	0	5.00	2.57	2.80	10.36	0.00436
Total	3651	0	3.40	1.72	1.78	6.90	0.00294

rapid changes have been observed (table 4) in some parishes, sometimes over long periods of time. This indicates that the trend is not due to accidents of sampling.

ESTIMATES OF INBREEDING RATES FOR THE DIFFERENT STATES, REGIONS AND BRAZIL AS A WHOLE

With the data of table 1 supplemented by the information not presented here (Freire-Maia, 1957a, b), we have calculated the mean coefficient of inbreeding for the dioceses in each State, and for the States. In some cases the coefficient is an estimate because a guess based on the probable rates of the zones with unknown degrees of inbreeding was introduced. For instance, the total rates shown for Goiás, Bahia and Maranhão are somewhat and differentially higher than those calculated from the available data, because the zones lacking information in our tables have been assumed to have more consanguineous marriages than the dioceses here reported (for Goiás, see Frota-Pessoa and Filgueiras, 1957). The Pernambuco estimate, however, is a little lower than the mean computed from the available data. The most probable rates for each of the five Brazilian regions were calculated from

the State means and, on the basis of regions, a general estimate has been obtained for the whole country. Table 5 summarizes the results with remarks on the probable degree of accuracy of each estimate given in footnotes.

All the estimates have been made on the basis of weighted means, using as weights, for the dioceses, the total number of marriages contracted per year in each one, and for the States and the regions, the appropriate 1950 populations. Since the regions with poorer information (North and West-central) have joint populations representing less than 7 per cent of the total Brazilian population, we are confident that our estimate for the whole country will not deviate very much from the true value.

The fact that the mean coefficient of inbreeding for contemporary Brazilian population is just a little higher than 0.002 may be very misleading if the great heterogeneity in the rate of inbreeding in the different zones (some of them presenting coefficients more than 10 times that of others) is not taken in account. About 40 per cent of the Brazilian population (South and part of the East) has an "European" inbreeding level. This explains why the Brazilian mean is relatively low, in spite of the fact that some regions are highly inbred from the modern point of view.

TABLE 3. FREQUENCIES OF CONSANGUINEOUS MARRIAGES IN THE STATE OF PERNAMBUCO (DIOCESE OF PETROLINA)

Localities	N	UNi + ANe	1C	1½-C	2C	T	α
Parnamirim, 1	155	0	13.55	2.58	11.61	27.74	0.01200
3	179	0	19.55	2.23	8.94	30.72	0.01563
Manacá, 1	196	0	9.69	4.08	5.10	18.88	0.00861
3	206	0.49	15.53	1.94	7.77	25.73	0.01388
Salgueiro, 1	209	0.96	13.40	4.31	9.09	27.76	0.01391
3	278	0.36	15.11	3.24	5.76	24.47	0.01265
Cruz de Malta, 2	55	0	10.91	1.82	3.64	16.36	0.00795
3	55	0	14.55	5.45	7.27	27.27	0.01222
Serrita, 1	102	0	20.59	2.94	3.92	27.45	0.01547
3	177	0	11.30	3.95	5.65	20.90	0.00945
Coripós, 1925	127	0	14.96	5.51	5.51	25.98	0.01255
3	133	0	11.28	3.76	4.51	19.55	0.00940
Petrolina, 1	351	0	9.97	1.99	3.13	15.10	0.00761
3	431	0	7.89	4.41	9.05	21.35	0.00866
Bodocó, 3	313	0.96	7.67	0.96	3.83	13.42	0.00699
Araripina, 1	311	0	10.61	2.57	5.14	18.33	0.00940
3	529	0.38	6.05	2.27	3.40	12.29*	0.00641
Cabrobó, 1	162	1.85	12.96	2.47	6.17	23.45	0.01379
3	178	0	7.30	3.37	3.37	14.04	0.00623
Ouricuri, 1	52	0	23.08	7.69	13.46	44.23	0.01983
3	179	0	6.15	1.68	3.35	11.17	0.00550
Exú, 3	322	0	6.83	2.18	1.24	10.25	0.00529
Granito, 1950	83	1.20	3.61	2.41	0	7.23	0.00452
Total (1)	1720	0.29	12.85	3.84	8.89	25.87	0.01098
Total (3)	3063	0.26	9.50	2.74	5.00	17.53†	0.00859

1—1925–1927; 2—1926–1927; 3—1950–1951.

* Including one marriage between niece and great uncle (0.19).

† Idem (0.03).

TABLE 4. FREQUENCIES OF CONSANGUINEOUS MARRIAGES IN SOME DIOCESES AND LOCALITIES

Dioceses (d) and localities (l)	Period	N	UNi + ANe	1C	1½C	2C	T	α
Florianópolis, SC (l)	1927–1931	568	0	0.88	0.18	0.18	1.24	0.00063
	1933–1941	599	0	0.83	0.33	0.50	1.66	0.00070
	1948–1951	1,135	0	0.09	0.09	0.17	0.35	0.00011
Goiás, Go (l)	1917–1937	600	0	3.17	0.33	1.67	5.17	0.00247
	1937–1945	342	0	2.34	0	1.46	3.80	0.00169
	1945–1950	348	0	0.86	0.57	2.30	3.73	0.00108
Belo Horizonte, MG (l)	1924–1930	570	0	1.93	0	1.05	2.98	0.00137
	1950–1952	790	0	0.38	0	0	0.38	0.00023
Coqueiral, MG (l)	1924–1929	161	0	6.83	1.86	4.97	13.66	0.00563
	1944–1947	268	0	6.72	5.22	2.61	14.55	0.00624
	1949–1951	219	0	4.57	4.57	4.57	13.70	0.00499
São Sebastião, SP (l)	1917–1921	69	0	1.45	0	1.45	2.90	0.00113
	1928–1936	300	0	3.00	0	0.33	3.33	0.00193
	1938–1942	159	0	3.77	0	2.52	6.29	0.00295
	1945–1952	250	0.40	2.00	0	1.60	4.00	0.00238
Ponta Grossa, Pr (d)	1933–1935	5,352	0.11	1.81	0.77	0.65	3.34	0.00167
	1936–1938	6,676	0.05	1.63	0.50	0.70	2.88	0.00135
	1939–1941	4,900	0.02	1.96	0.63	0.92	3.53	0.00162
	1942–1944	6,914	0.04	1.95	0.54	0.80	3.33	0.00163
	1945–1947	7,590	0	1.80	0.70	0.78	3.28	0.00149
	1948–1950	8,242	0.01	1.25	0.66	0.76	2.68	0.00118
	1951–1953	7,757	0.06	1.11	0.48	0.72	2.37	0.00106
Curitiba, Pr (l)	1850–1851	120	0	2.50	3.33	0	5.83	0.00260
	1865–1866	137	0	1.46	2.92	0.73	5.11	0.00194
	1870–1872	291	0.69	4.47	4.47	2.06	11.68	0.00537
	1873–1874	149	0.67	2.01	2.01	0.67	5.37	0.00283
	1890–1891	386	0.26	1.29	0.52	0.52	2.59	0.00138
	1908–1909	252	0	0.79	0	0.79	1.58	0.00062
	1910–1911	318	0	0.63	0	0.63	1.26	0.00049
	1931–1932	580	0	1.03	0	0.35	1.38	0.00070
	1945–1951	7,298	0	0.49	0.22	0.21	0.92	0.00041
Itajaí, SC (l)	1897–1899	192	0	2.60	0	0.52	3.13	0.00171
	1914–1916	237	0	4.21	1.27	1.69	7.17	0.00330
	1941–1942	444	0	0.68	0	0.45	1.13	0.00049
	1950–1951	589	0.17	0.68	0.51	1.36	2.72	0.00101
Mogi das Cruzes, SP (l)	1788–1800	444	0	0.45	0.45	0	0.90	0.00042
	1802–1809	333	0	0.60	0.90	1.20	2.70	0.00084
	1812–1821	394	0.25	0.76	1.27	0.76	3.05	0.00131
	1821–1829	301	0	2.33	1.00	2.99	6.31	0.00223
	1829–1835	272	0.73	4.78	1.47	5.15	12.13	0.00517
	1838–1845	285	1.05	6.67	2.11	3.51	13.33	0.00669
	1845–1850*	200	1.50	7.00	5.00	4.50	18.00	0.00852
São Paulo city (parish of Sta. Efigênia)	1809–1826	220	0.45	2.73	0.91	1.82	5.91	0.00284
	1836–1855*	238	5.46	5.04	1.68	3.36	15.55	0.01103
São Paulo (the whole city)	1826–1859	1,053	3.04	6.93	1.62	4.84	16.43	0.00939
	1939–1950	37,447	0.01	0.66	0.12	0.16	0.95	0.00049
Vacaria, RGS (prelacy)	1939	754	0	1.46	0	0.93	2.39	0.00106
	1951	1,026	0	1.37	0.29	0.78	2.44	0.00107
	1952	930	0	1.40	0.65	1.18	3.23	0.00128
	1953	997	0	2.51	0.50	1.00	4.01	0.00190
	1954	1,163	0	2.58	0.26	1.03	3.87	0.00185
Regente Feijó, SP (l)	1931–1936	590	0	0.51	0	0.17	0.68	0.00034
	1955	170	0	0.59	0	0	0.59	0.00037
Presidente Prudente, SP (l)	1925–1929	597	0	0.67	0.17	0.33	1.17	0.00058
	1952-1956	973	0	0.82	0.10	0	0.92	0.00061

* From this time up to the present, a decrease of the inbreeding rates has been observed (cf. Freire-Maia, 1952).

TABLE 5. ESTIMATES OF INBREEDING RATES FOR THE BRAZILIAN STATES AND REGIONS AND FOR THE WHOLE BRAZILIAN POPULATION IN RECENT YEARS

State and region	UNi + ANe	1C	1½C	2C	T	α
Rio Grande do Sul (2)*	0.02	1.25	0.35	0.80	2.42	0.00104
Santa Catarina (1)	0.02	1.10	0.40	1.00	2.52	0.00099
Paraná (1)	0.02	1.00	0.30	0.60	1.92	0.00084
São Paulo (1)	0.02	0.85	0.20	0.30	1.37	0.00067
Minas Gerais (2)	0.03	3.60	1.45	2.00	7.08	0.00305
Rio de Janeiro (2)	0.02	1.25	0.40	0.35	2.02	0.00099
Distrito Federal (2)	0.01	0.50	0.15	0.20	0.86	0.00040
Espírito Santo (4)	0.03	2.00	0.60	1.00	3.63	0.00163
Bahia (2)	0.02	4.80	1.65	2.85	9.32	0.00399
Sergipe (1)	0.10	4.00	0.60	1.70	6.40	0.00308
Alagoas (1)	0.10	3.50	0.90	1.80	6.30	0.00288
Pernambuco (1)	0.06	4.00	1.30	2.30	7.66	0.00334
Paraiba (3)	0.08	4.50	1.50	2.50	8.58	0.00377
Rio Grande do Norte (3)	0.06	3.50	1.10	2.00	6.66	0.00292
Ceará (2)	0.10	5.00	1.50	2.50	9.10	0.00411
Piaui (3)	0.10	5.00	2.00	3.50	10.60	0.00442
Maranhão (4)	0.08	4.50	1.50	3.00	9.08	0.00385
Pará (4)	0.04	2.00	0.80	1.20	4.04	0.00174
Amazonas (4)	0.05	2.50	1.00	1.50	5.05	0.00217
Goiás (4)	0.03	2.50	1.00	1.50	5.03	0.00215
Mato Grosso (3)	0.04	3.00	1.20	1.80	6.04	0.00258
South (1)	0.02	1.00	0.26	0.52	1.80	0.00081
East (2)	0.02	2.30	0.80	1.28	4.40	0.00191
North-East (2)	0.08	4.35	1.42	2.50	8.35	0.00365
North (4)	0.04	2.20	0.86	1.30	4.40	0.00190
Center-West (3)	0.03	2.65	1.07	1.60	5.35	0.00228
Brazil (2)	0.04	2.40	0.77	1.35	4.56	0.00200

* Approximate degrees of accuracy: (1) high, (2) fair, (3) low, and (4) poor.

No calculation is presented for the territories, whose populations represent, in all, less than 0.04% of the total Brazilian population.

The estimates for the State of Espirito Santo has been made on the basis of the data for the neighbor zones belonging to the other states.

The estimates for the Distrito Federal, that includes the city of Rio de Janeiro (to be not confused with the State of the same name), have been made not only on the basis of the data at our disposal and referring to one of its parishes, but also taking into consideration the values obtained for the city of São Paulo, approximately of the same population size.

These estimates do *not* refer to contemporary populations, but only to marriages contracted in recent times.

DISCUSSION

Factors of the geographic distribution

It is difficult to evaluate the specific factors which account for the differences in inbreeding rates in various parts of Brazil. The socioeconomic features of the South (sometimes referred to by sociologists as the "new Brazil") are, however, quite different from those characterizing the other four physiographic regions taken together (called "old Brazil", Fig. 1). From an analysis of the problem (a full account of which will be published elsewhere), it is concluded that cultural pattern, economic level, migration, population density, and degree of ruralization are the most effective factors acting on inbreeding levels in Brazil. While it is not possible to isolate any one of these factors completely, some notion of their individual contributions can be obtained. Figures 2 and 3 present two examples where this is possible. It is seen, for instance, that socio-economically different populations may show large differences in inbreeding rates even when they have the same demographic density (Fig. 2) or the same ruralization index (Fig. 3).

The trends in time

The "normal" secular trends, found in so many populations, reflect the growth of isolate size in two different ways, namely, the expansion of previous boundaries, and the break-up of these same boundaries through migration (Dahlberg, 1938). As both of these phenomena present increasing rates and wider and wider geographic distribution in the modern world, inbreeding rates would be expected to show the de-

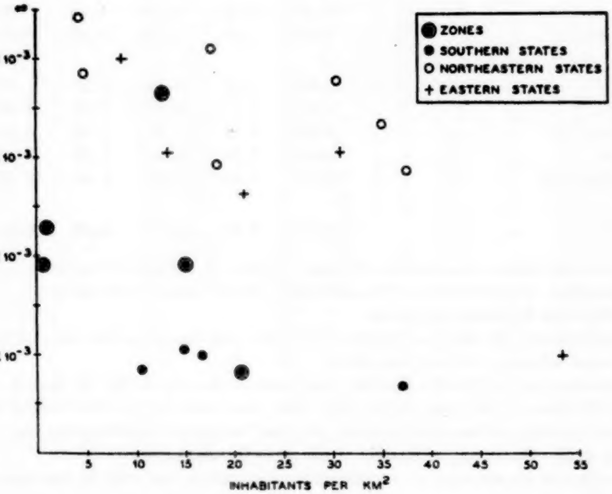

FIG. 2. NEGATIVE ASSOCIATION BETWEEN COEFFICIENT OF INBREEDING AND POPULATION DENSITY. DATA ARE GIVEN FOR THE FIVE BRAZILIAN ZONES AND FOR EACH ONE OF THE STATES IN THE THREE ZONES WITH MORE ACCURATE ESTIMATES OF INBREEDING COEFFICIENTS.

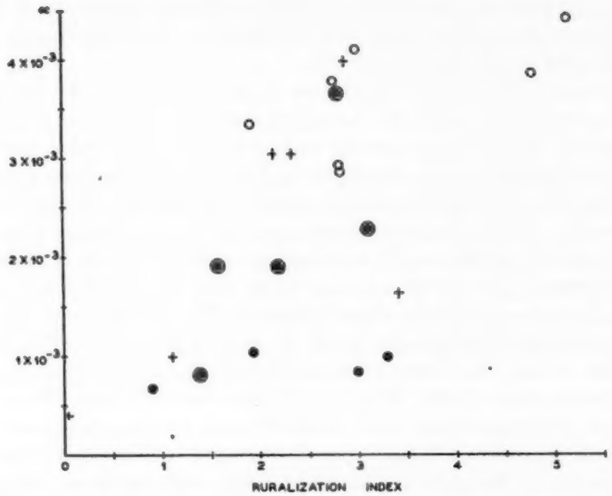

FIG. 3. POSITIVE ASSOCIATION BETWEEN COEFFICIENT OF INBREEDING AND "RURALIZATION INDEX" (SYMBOLS IDENTICAL TO THOSE OF FIG. 2). "RURALIZATION INDEX" IS THE RATIO OF THE RURAL PART OF THE POPULATION TO THE URBAN ONE. RURAL IS HERE DEFINED ON THE DOMICILAR AND NOT OCCUPATIONAL POINT OF VIEW.

creasing feature commonly seen. Unusual reversed trends found in a few localities and regions in the last as well as in the present century (table 4) probably reflect the reversed action of socio-economic factors previously analysed. Only historic research could throw light on this problem. It is interesting to point out that Ellis (1936), in his studies based on genealogical data gathered by Silva Leme, also detected increasing inbreeding among the upper class in São Paulo during the last century and that, in France, one department also showed a similar "reversed" trend during about 30 years in the first half of the 19th century (Sutter and Tabah, 1955).

Isolate sizes

Although the first attempt to estimate isolate sizes was made in the year of the "rediscovery" of the Mendelian laws (Raseri, 1900), the genetic implications of the concept were not fully realized until some decades later.

Several attempts have been made in the last years to obtain a quantitative evaluation of the problem using direct or semi-direct methods generally in religious or ethnic isolated communities (Birdsell, 1950, 1953; Glass *et al.*, 1952; Lasker, 1952, 1954; Malaurie, Tabah, and Sutter, 1952; Spuhler and Kluckhohn, 1953; Schull, 1953; and Kraus and White, 1956) as well as indirect methods in general populations (Dunn, 1947; Sutter and Tabah, 1951; Freire-Maia, 1951, 1952; Böök and Mawe, 1955; Böök, 1956; Frota-Pessoa, 1957; Cavalli-Sforza, 1957; and Fraccaro, 1957). This second approach, developed by Dahlberg (1938), is based on the assumption

that consanguineous marriages occur at random, which is known not to be true and thus involves an error whose magnitude is difficult to evaluate correctly (*cf.* discussion of the problem in Morton, 1955).

Frota-Pessoa (1957) showed that the use of the value b (i.e., the average number of children who become adult and marry per marriage) introduces a certain degree of inaccuracy in the Dahlberg formula and leads to an appreciable lowering of the results. The corrected formula, developed by Frota-Pessoa, has been applied by him to the situation in three Brazilian states, namely, Pernambuco, Alagoas and Paraná. The frequencies of first cousin marriages used are those presented here. (The fact that the frequencies of first cousin marriages are more influenced by population size than by migration (the reverse situation being true for second cousin marriages), according to recent research by Cavalli-Sforza (1957), brought new support to the idea that estimates of isolate sizes based on the first parameter will probably give more reliable values than those obtained through the incidence of second cousin matings.) Isolate sizes of 900, 980 and 3,752 have been obtained. These values are about 50 per cent higher than those calculated using Dahlberg's formula. Assuming that the same approximate relation prevails for all Brazilian populations, then the mean isolate size in Brazil would be about 1,500, with the lowest values in some zones of the Eastern and Northeastern regions (about 390) and the highest value in the Southern states (about 4,000). The previous estimate of the mean isolate size in Brazilian populations as 500 or less (Freire-Maia, 1951, 1952) is certainly too low not only because it was obtained through the use of Dahlberg's formula but also because it was based on too high an estimate of first cousin marriage.

The present values, naturally, are not to be compared to those calculated through the classical Dahlberg formula which uses the frequency of first cousin marriage, or that employed by Sutter and Tabah (1951) which is based on the incidence of marriage between second cousins.

Ludwig and Schelling (1948) devised a formula to estimate the coefficient of inbreeding from the number of sexually mature couples (N) in the population, and the degree of stability of these couples (g), where g may vary from 0, when the couples separate after the conception of a child, to 1, when each individual has a single monogamous marriage. Assuming that the above mentioned isolate sizes represent 2N individuals, the resulting estimates (for g = 0.8–1.0) are about one-third of those calculated on the basis of consanguineous marriages (table 6). Due to the errors involved in the estimates of the parameters, it is our opinion that the agreement is good between the two sets of estimates.

Different approaches to the concept of isolate size have been presented by other authors. The upper limit of the number of mates available for a reproductive in-

TABLE 6—ESTIMATES OF COEFFICIENTS OF INBREEDING BASED ON ISOLATE SIZES

Population	Isolate sizes	Calc. based on cons. marriages (A)	Calc. based on isolate sizes (B)		A/B	
			g = 1.0	g = 0.8	g = 1.0	g = 0.8
Pernambuco	900	0.00334	0.00111	0.00100	3.0	3.3
Alagoas	980	0.00288	0.00102	0.00092	2.8	3.1
Paraná	3,752	0.00084	0.00027	0.00024	3.1	3.5
South	4,000	0.00081	0.00025	0.00023	3.2	3.5
Northeast (central)	390	0.00794	0.00257	0.00231	3.1	3.4

dividual selected at random in a medium-sized American city, through consideration of only isolation by distance (so neglecting all the other factors) has been, for instance, calculated by Spuhler and Clark (1956). This approach was inspired by the concepts developed for animals and plants by Sewall Wright (1943, 1946). Some idea of the relative isolate sizes of different communities can also be obtained through the calculation of the "mean matrimonial radius" (*cf.*, for instance, Schwidetzky, 1955). This simpler approach is subject to a greater number of limitations than the previous one, because no consideration is given to population density. Another estimate, also subject to several limitations, may be obtained through the use of the exogamy index (Freire-Maia, 1951, 1952). With the collaboration of A. Freire-Maia, these methods have been applied to a number of Brazilian populations, from small villages to large cities, and from rapidly developing rural zones with their new and fast growing communities to old regions and their socio-economically stagnated towns. The results, not yet complete, will be published elsewhere.

SUMMARY

An analysis is made of the incidence of consanguineous marriages in about 60 dioceses distributed among almost all the Brazilian States. Some of the inbreeding levels found are the highest known up to the present time. However, the Southern States present relatively low coefficients of inbreeding. Several examples of geographic gradients and trends in time are presented. Estimates of mean incidence of consanguineous marriages are calculated for each Brazilian State and for the whole country. The problem of isolate size is briefly discussed.

ACKNOWLEDGMENTS

This research was possible only through the kind cooperation of a large number of Bishops and Priests who sent me information regarding the incidence of consanguineous marriages in their dioceses, prelacies and parishes or permitted me to examine books and other documents in their files. My thanks are also due to the directors of the Faculty of Philosophy of the University of Paraná (Dr. Homero de Barros) and of the Faculty's Research Institute (Dr. J. Loureiro Fernandes); to the Brazilian National Research Council, to the CAPES (in the person of Dr. Rudolph T. Atcon), and to the Rockefeller Foundation (in the person of Dr. Harry M. Miller, Jr.); to Drs. James V. Neel, J. N. Spuhler, William J. Schull, and O. Frota-Pessoa; to Dr. Homero Braga, Father Jesus S. Moure CMF, and Ademar Freire-Maia, L. Sc.; to Miss Rosa Miltes Vendramin, Miss Wally M. T. Beltrami, Miss Grace Yesley, and Mrs. Harriet May.

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Gene Flow from White into Negro Populations in Brazil

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GLASS AND LI (1953) have introduced a statistical model that allows calculations to be made, not only of the intermixture between two base populations but also of the dynamic pattern of the gene flow from one population to another, during a known period of intermixture. The formula derived from Glass and Li is:

$$(1 - m)^k = \frac{q_k - Q}{q_0 - Q}$$

To use this formula it is necessary to know: a) the gene frequencies, q_0 and Q, of the base populations; b) the gene frequency, q_k, of the hybrid population; and c) the number of generations, k, of contact between the base populations. The average rates of gene flow (m) from one population to another varies according to the assumed value of k and to the amount of accumulated admixture in the hybrid population. Some limitations of this method have been stressed by Glass and Li.

It should be of interest to compare the process of hybridization between Negro and White populations in Brazil to that in the United States, since the social conditions in the two countries have been and still are different. This is a first attempt to do so.

THE BRAZILIAN NEGRO

An important problem, which is not yet completely settled, is the African origin of Brazilian Negroes. The comparative ethnography of the Brazilian Negro was worked out, in its fundamental aspects, by the pioneer work of Nina Rodrigues (1932) and the later work of Ramos (1951a). The data on the relations between African and Brazilian cultural groups of Negroes shown in Table 1 result from these studies.

Table 1 shows that the Negroes who arrived in Brazil belonged to two main groups:

Bantu stock. This group is spread throughout Brazil. It is represented chiefly by the "Angola-Congolês" group from Angola and Congo, and to a lesser extent, by the "Contra-Costa" group from Moçambique. The Bantus settled in several places: in the States of Maranhão and Pará, from where they migrated to the inner part of Pará; in the States of Pernambuco and Alagoas, from which they migrated to the State of Ceará; and in the States of Rio de Janeiro, São Paulo and Minas Gerais, from where they migrated to the State of Goiás.

Sudanese stock. This group settled in the State of Bahia. The bulk of it is represented by the Ashanti from the Gold Coast, the Ewe from Dahomey, and chiefly

Received May 27, 1957.

TABLE 1. RELATIONS BETWEEN THE CULTURAL GROUPS OF AFRICAN AND BRAZILIAN NEGROES (BASED ON DATA BY RAMOS, 1951a)

African Cultural Group		Geographical Distribution in Africa	Culture Group Related in Brazil	Early Geographical Distribution in Brazil	Probable Time of First Arrival in Brazil	Remarks
Major groups	Subgroups					
I—Guinean-Sudanese Culture	Fulah Mandinga Houssah	Northern Sudan Senegal Guinea, Western and Central Sudan	"malê"	mainly in Bahia	beginning of the 17th century	Mahometan Negroes under Semitic and Hamitic influence. Small traffic to Brazil
II—Sudanese Culture	Fanti-Ashanti Ewe Yoruba	Gold Coast Dahomey Nigeria (mainly Southern)	Mina Gegê Nagô	Bahia	beginning of the 17th century beginning of the 19th century	Intense traffic bounded upon small area in Brazil. Mainly represented by Yoruba
III—Bantu Culture	Western group Eastern group	Congo, Angola Moçambique, Tanganika, Lakes' region, etc.	"Angola-Congolês" "Contra-Costa"	Rio de Janeiro, S. Paulo, Maranhão, Pernambuco, Alagoas	In the middle of 16th century	Culture group but linguistic. Heterogeneous stock under Hamitic influence. Intense traffic

FIG. 1. Early settlements of African Negroes in Brazil and their further migrations (after Ramos 1951b, modif.)

the Yoruba from Nigeria (especially southern Nigeria). The Sudanese came in smaller numbers than the Bantus. The geographical distribution of the Bantus and the Sudanese overlaps to some extent in Brazil.

The above data, although somewhat inaccurate, may still be used for determining the present race admixture in Brazil. Figure 1 shows the places of early settlements of Negro slaves in Brazil and their subsequent migrations.

Another problem of interest is the determination of the ratio of Negro to White people in Brazil. The relative number of Negroes has changed in time. Before considering this change it is necessary to point out that in the Brazilian census a distinction is made between the full Negroes (called Negroes) and the lighter Negroes (Mulattoes). The total number of slaves introduced in Brazil is calculated to be about 18 million, which amounts to five to six million per century. The relative ethnic composition at three periods in Brazil, according to the censuses of 1798 (unofficial; cf. Ramos, 1951a), 1872 and 1950 are:

Year	Total population	Whites (%)	Negroes (%)	Mulattoes (%)
1798	3,250,000	39.0	54.0	7.0
1872	9,930,479	38.1	19.7	38.3
1950	51,944,397	61.6	10.9	22.5

TABLE 2. GENE FREQUENCIES OF RH TYPES AMONG AFRICAN NEGROES, BRAZILIAN NEGROES AND BRAZILIAN WHITES

	No.	$R^0(cDe)$	$R^1(CDe)$	$r(cde)$	Reference
			African Negroes		
Sudan Group					
Ewe	161	.480	.086	.235	Armattoe, Ikin & Mourant, 1953
Ashanti	113	.558	.120	.230	Armattoe, Ikin & Mourant, 1953
S. E. Nigeria	106	.563	.046	.238	Chalmers, Ikin & Mourant, 1953
S. W. Nigeria	145	.602	.058	.184	Chalmers, Ikin & Mourant, 1953
N. Nigeria	165	.539	.099	.136	Chalmers, Ikin & Mourant, 1953
Jos Plateau	124	.568	.007	.243	Chalmers, Ikin & Mourant, 1953
N. Sudanese	133	.461	.016	.237	Brooks, Garner, Ikin & Mourant, 1952
Average	947	.539	.062	.215	—
Bantu Group					
S. Afr. Bantu	644	.649	.027	.118	Shapiro, 1953
			Brazilian Negroes		
Bahia	326	.398	.160	.257	Pedreira, 1954
S. Paulo	277	.281	.242	.325	Ottensooser, Lacaz, Ferreira & Mellone, 1948
Rio de Janeiro	153	.399	.332	.318	Lopes & Junqueira, 1952
			Brazilian Whites		
Bahia	174	.068	.424	.347	Pedreira, 1954
S. Paulo	138	.068	.406	.390	Ottensooser, Lacaz, Ferreira & Mellone, 1948
Rio de Janeiro	605	.064	.420	.414	Lopes & Junqueira, 1952

In the southern states of Brazil, Negro-White intermixture should have occurred intensely until about 1872. By this time the migration of several European peoples other than Portuguese had begun, especially to the southern part of the country. These migrants have shown a greater resistance to crossing with the Negroes than have the Portuguese. The European migratory movements in the last century have contributed to the increase of the relative number of Whites in the census of 1950.

ESTIMATION OF GENE FLOW

The number of generations of Negro-White contact. According to Ramos (1951a), the date on which the first slaves arrived in Brazil is uncertain. There are some indications that slave trade in Brazil began in 1538, with the arrival of a small group of Negroes at Rio de Janeiro. The most intense traffic was from the 16th up to the 19th century (Taunnay, 1941). It is reasonable to postulate that the period of Negro-White contact in Brazil is about 350 years.

In order to ascertain the number of generations of intermixture (k) it is necessary to know the average length of a generation at the present time. According to the Brazilian Census (Mortara, 1947), the average age of mothers (including Negro

Table 3. Gene frequencies of the sensitivity to phenylthiourea among African negroes Brazilian negroes and Brazilian whites

Sample	Number	Taste Gene Freq.	Reference
African Negroes (W. Africa)	57	.813	Barnicot, 1950
Brazilian Negroes (S. Paulo)	115	.687	Saldanha (unpublished)
Brazilian Whites (Rio de Janeiro)	164	.448	Saldanha & Guinsburg, 1954

Table 4. Gene frequencies of ABO blood groups among African negroes, Brazilian negroes and Brazilian whites

	No.	I^A	I^B	i	Reference
			African Negroes		
Sudan Group					
Ewe	161	.151	.169	.680	Armattoe, Ikin & Mourant, 1953
Ashanti	113	.148	.138	.714	Armattoe, Ikin & Mourant, 1953
S. E. Nigeria	106	.071	.079	.779	Chalmers, Ikin & Mourant, 1953
S. W. Nigeria	145	.064	.128	.744	Chalmers, Ikin & Mourant, 1953
N. Nigeria	167	.080	.157	.683	Chalmers, Ikin & Mourant, 1953
Jos Plateau	124	.069	.148	.714	Chalmers, Ikin & Mourant, 1953
N. Sudanese	133	.172	.145	.683	Brooks, Garner, Ikin & Mourant, 1952
Yoruba	325	.133	.143	.724	Cf. Glass & Li, 1953; table 4
Senegalese	238	.140	.192	.680	Cf. Glass & Li, 1953; table 4
Average	1512	.114	.144	.733	—
Bantu Group					
S. Afr. Bantu	6020	.190	.130	.680	Shapiro, 1951
Bas Congo	357	.153	.120	.727	Lambotte-Legrand & Lambotte-Legrand, 1950
Angola	2246	.157	.140	.703	David, 1949
Average	8623	.167	.130	.703	—
			Brazilian Negroes		
Bahia I	7967	.165	.100	.735	Novais, 1953
Bahia II	326	.178	.063	.759	Pedreira, 1954
Average	8293	.172	.082	.747	—
S. Paulo I	277	.181	.115	.703	Faria & Ottensooser, 1951
S. Paulo II	3429	.172	.114	.712	Mellone, Ludovici, Maluf & Macruz, 1952
Average	3706	.177	.115	.708	—
			Brazilian Whites		
Bahia I	4248	.223	.067	.708	Novais, 1953
Bahia II	174	.285	.026	.687	Pedreira, 1954
Average	4422	.254	.047	.698	—
S. Paulo I	3978	.241	.069	.689	Faria & Ottensooser, 1951
S. Paulo II	12494	.230	.071	.698	Mellone, Ludovici, Maluf & Macruz, 1952
Average	16472	.236	.070	.694	—

TABLE 5. FREQUENCIES OF GENES OF THE NEGRO AND WHITE BASE POPULATIONS, PERCENTAGE OF WHITE ADMIXTURE AND AVERAGE RATES OF GENE FLOW FROM WHITE INTO NEGRO POPULATIONS, CONSIDERING THE TWO EARLY MAIN GROUPS OF NEGROES IN BRAZIL: BANTU AND SUDANESE (ASSUMING K = 12).

Gene	African Negroes (q_s)		Brazilian Negroes (q_k)		Brazilian Whites (Q)		Difference (q_o − Q)	White Admixture (%)	Average Gene Flow (m)
R^0	Bantu Group (1)	.649	S. Paulo	.281	S. Paulo	.068	.581	63.34	.0803
(*cDe*)	Sudan Group (2)	.539	Bahia	.398	Bahia	.068	.471	29.94	.0292
R^1	Bantu Group (1)	.027	S. Paulo	.242	S. Paulo	.406	.379	56.73	.0676
(*CDe*)	Sudan Group (2)	.062	Bahia	.160	Bahia	.424	.362	27.08	.0261
Taste gene	W. Africa	.813	S. Paulo	.687	Rio Jan.	.448	.365	34.53	.0354
r (*cde*)	Bantu Group (1)	.118	S. Paulo	.325	S. Paulo	.390	.272	76.11	.1126
	Sudan Group (2)	.215	Bahia	.257	Bahia	.347	.132	31.82	.0314
I^A	Bantu Group (2)	.167	S. Paulo	.177	S. Paulo	.236	.069	14.48	.0121
	Sudan Group (2)	.114	Bahia	.172	Bahia	.254	.140	40.15	.0419
I^B	Bantu Group (2)	.130	S. Paulo	.115	S. Paulo	.070	.060	25.00	.0238
	Sudan Group (2)	.144	Bahia	.082	Bahia	.047	.097	65.05	.0839

1. S. Africa Bantu 2. Average frequency

and White) at the birth of their children during the year of 1940, is 28.6 years. The corresponding figure for fathers is not available, but must be greater than that for the mothers, since men marry later than women. The length of a generation has, therefore, to be taken as somewhat higher than 28.6 years, a convenient estimate being 30 years.

The gene frequencies of the base populations. It is necessary to know the gene frequencies of the base and the hybrid populations in order to calculate the average gene flow from White into Negro populations. The studies on gene frequencies of Brazilian Negro populations are few. We used data on genes for the Rh types, R^0 (*cDe*), R^1 (*CDe*) and *r* (*cde*), for sensitivity to phenylthiourea (taste gene *T*), and for ABO blood groups (I^A and I^B). The corresponding frequencies appear in table 5 in order of decreasing value of their differences in the base populations. Other genes, whose frequencies in the base populations differed by less than 10 per cent were not used. Since Brazilian Negroes seem to originate from two different African stocks, Bantu and Sudanese, separate calculations were made for each of them. For the Rh gene frequencies (table 2) and for the average of the frequencies of the ABO genes (table 4), data found by several investigators were used as representing the frequencies for each group. For the taste gene (table 3) only one sample (Barnicot, 1950), from West Africa, was available. The data available on gene frequencies of Brazilian Negroes discriminate between full Negroes and Mulattoes. Since these people belong to the same populations, their average gene frequencies were used as representing the Brazilian Negro.

In the Rh system, the frequencies of the D^u gene were not considered, since this gene may be classified as *d* and its frequency among Whites is negligible (Mourant, 1954). The *r* (*cde*) gene frequencies for the Mulattoes of the State of Rio de Janeiro has been used instead of that for Mulattoes plus Negroes because the number of individuals in the Negro sample classified as Rh negative *rr* (*cde/cde*) is too small and the

corresponding gene frequency is lower than that of the African Negro. This is probably due to the small number of full Negroes tested.

The taste thresholds for phenylthiourea sensitivity (table 3) were determined for a sample of Brazilian Whites (Saldanha and Guinsburg, 1954) and for a sample of Brazilian Negroes by the author (unpublished). In both cases the thresholds were measured according to the technique described by Harris and Kalmus (1949). Calculations based on phenylthiourea sensitivity were possible only for the State of São Paulo.

The gene frequencies of ABO blood groups were recalculated by Fisher's new method (cf. Race and Sanger, 1950) since the calculations by Bernstein's method

TABLE 6. PERCENTAGE OF WHITE ADMIXTURE AND AVERAGE RATES OF GENE FLOW PER GENERATION FROM WHITE INTO NEGRO POPULATIONS, CALCULATED FROM THE FREQUENCIES OF GENES OF THE RH BLOOD SYSTEM IN DIFFERENT AFRICAN SAMPLES (ASSUMING K = 12)

African Samples	Brazilian Samples					
	Bahia		S. Paulo		Rio de Janeiro	
	White admixture (%)	Gene flow	White admixture (%)	Gene flow	White admixture (%)	Gene flow
			R^0 (*cDe*)			
Ewe	19.91	.0184	48.31	.0535	19.48	.0180
Ashanti	32.66	.0326	54.90	.0643	32.19	.0317
S. E. Nigeria	33.34	.0332	56.97	.0680	25.39	.0243
S. W. Nigeria	38.20	.0394	60.12	.0738	37.74	.0388
N. Nigeria	29.96	.0292	54.78	.0641	29.48	.0288
Jos Plateau	34.00	.0341	57.40	.0686	33.54	.0335
N. Sudanese	16.04	.0146	45.78	.0498	15.62	.0141
S. Afr. Bantu	43.21	.0461	63.34	.0803	42.57	.0452
			R^1 (*CDe*)			
Ewe	21.87	.0205	60.96	.0791	73.66	.1052
Ashanti	13.16	.0119	42.66	.0454	73.00	.1033
S. E. Nigeria	30.43	.0299	54.45	.0635	76.48	.1136
S. W. Nigeria	27.87	.0270	52.86	.0609	75.70	.1112
N. Nigeria	18.77	.0177	46.58	.0509	72.59	.1023
Jos Plateau	36.70	.0375	58.90	.0714	78.70	.1209
N. Sudanese	35.30	.0357	57.95	.0697	78.22	.1193
S. Afr. Bantu	33.51	.0335	56.73	.0676	77.61	.1173
			r (*cde*)			
Ewe	19.65	.0182	58.07	.0699	46.37	.0507
Ashanti	23.08	.0216	59.38	.0725	47.81	.0528
S. E. Nigeria	17.44	.0159	57.24	.0684	45.46	.0493
S. W. Nigeria	44.79	.0483	68.45	.0917	58.27	.0703
N. Nigeria	57.35	.0686	74.41	.1075	65.47	.0848
Jos Plateau	13.47	.0121	55.79	.0658	43.86	.0469
N. Sudanese	18.19	.0166	57.53	.0688	45.77	.0498
S. Afr. Bantu	60.74	.0750	76.11	.1126	70.38	.0975

are not suitable for studies of race admixture (Boyd, 1950). The frequencies of the ABO genes in the base populations are not very suitable for calculating the gene flow because their difference in these populations is small (table 5).

The average values of gene flow. The estimations of gene flow were calculated for the States of Bahia, São Paulo and Rio de Janeiro. It was postulated that the direction of the gene flow is from White into Negro populations only. This is not completely true, as is stressed by Glass and Li (1953) in the study of the American Negro.

The gene flow was calculated first by using the gene frequencies of the Sudanese Negroes for the State of Bahia and those of the Bantu Negroes for the States of São Paulo and Rio de Janeiro (table 5). However, as both African stocks have, in part, spread throughout Brazil, calculations were also made for each of the three States based on the frequencies of the Bantu sample and various Sudanese samples.

The results presented in this paper are only tentative because further studies on the origins of the Brazilian Negro may change the present views, upon which our calculations are based.

Table 6 gives various estimates of the accumulated White admixture in Brazilian Negro as well as the gene flow from White into Negro populations in three States of Brazil. The figures are higher for the States in which Negroes have a Bantu ancestry (São Paulo and Rio de Janeiro) than for the State in which they have a Sudanese ancestry (Bahia).

The modal values of percentage of White admixture and average gene flow from White into Negro populations are:

Place	White admixture (%)	Gene flow (m)
Bahia	ca. 35	.035-.040
São Paulo, Rio de Janeiro	ca. 55	.060-.065
Brazil	ca. 40	.045-.050

DISCUSSION

The gene flow to the Negro population of Bantu origin (in São Paulo and Rio de Janeiro) is roughly twice as great as that calculated for the Negroes of Sudanese origin (in Bahia). However, there is some indication that the Negroes introduced into Bahia were not exclusively of Sudanese ancestry.

Sudanese Negroes who settled in Bahia are mainly represented by people of Yoruba culture (see table 1) from South Nigeria (Ramos, 1951a). It is believed they have arrived at Bahia during the beginning of 19th century. Therefore, the time of intermixture with Whites is for this Negro group decreased to about 150 years, that is, 5 generations. The intermixture which occurred before that time must have taken place between the White and Bantu groups which were introduced in Brazil at the beginning of the 16th century. By recalculating the amount of White admixture and average gene flow from the White into the Negro populations in the State of Bahia, using the R° (*cDe*) gene frequencies of Yoruba (S. W. Nigeria) and South Africa Bantu independently, we get the figures: 39 per cent, m = .094 and 47 per cent, m = .051, assuming k = 5 and k = 12 respectively. Probably the correct figures should be intermediate between these.

The values of accumulated admixture and average gene flow are in general higher for Brazil than for the United States (Roberts, 1955). This difference is not difficult to explain. In Brazil hybridization is increasing more and more in recent times, following the slave freedom law. In the United States the situation has not changed much since the time of slavery as evidenced by the small number of Negro-White official marriages. In Brazil these cases are very numerous, especially in the Northern States of Bahia and Maranhão. However, the frequency of hybridization is probably variable in Brazil, according to the States, as a consequence of the different attitude towards intermixture of the European immigrants settling in different places. Portuguese, in contrast to most Europeans, are very fond of crossbreeding.

It is probably that the Brazilian Negroes are subjected to ecological and social forces which differ from those acting upon the Negroes in the United States. This can lead to selective forces of different intensity in the two countries. Unfortunately, it is difficult to discriminate between the frequency oscillation caused by gene flow and that caused by natural selection. An influence exerted by natural selection must be found by comparing gene flow for different gene loci in the same population. There is an indication of the action of selective forces if two estimates based on different genes differ appreciably.

Haldane (1942) and Wiener (1942) have noticed that the intrauterine selection against the heterozygotes (*Dd*) of the Rh system due to erythroblastosis fetalis must decrease the frequency of the rarer gene in the population. This selective process becomes apparent when a decrease of the *r* (*cde*) allele in Negro hybrid populations is detected. Glass (1950), however, found that this allele is becoming commoner among the United States Negroes. This has been explained as being caused by a compensatory increase of fertility in families with mother-fetus incompatibility. The estimates for Brazil of average gene flow derived from *r* (*cde*) allele do not differ from those derived from other genes. However, in the State of Bahia, the Mulattoes show a relatively lower frequency of this allele than is found among the full Negroes and Whites (these frequencies in Bahia are .390 for Whites, .273 for Negroes, and .242 for Mulattoes, according to Pedreira, 1954).

In the present paper no consideration has been given to the Negro-Amerindian intermixture. Glass (1955) has shown that Indians have not contributed appreciably to the gene frequencies of the United States Negroes. This conclusion probably does not apply for every Brazilian State. Intermixture between Negroes and Indians probably occurred to a considerable extent in the Northern States, mainly in Ceará and Maranhão. In Maranhão, for example, the ABO gene frequencies found among Mulattoes differ from the expected values calculated by considering only Negro-White crosses (see Silva, 1948). This discrepancy might be explained by taking into account the Indian contribution to the intermixture. In the Southern States, however, the Indian contribution was negligible and probably does not influence the accuracy of the data calculated in this paper.

SUMMARY

The average gene flow per generation from White into Negro populations in Brazil was calculated by Glass and Li's method. The modal values are .045–.050, assuming 12

generations of intermixture, and the White admixture accumulated in the Negro population is about 40%. Data from Sudanese and Bantu African Negroes, from which the Brazilian slaves originated, were used, for calculating gene flow and White admixture for three different States, according to the African origin of the early settlements of Negroes in Brazil. Variable estimates were found that must be due to the different number of generations of contact between Sudanese and Bantu Negro groups with the Whites in different states.

ACKNOWLEDGEMENTS

The author is indebted to Dr. O. Frota-Pessoa for his valuable suggestions and critic review of the manuscript.

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Phenylalanine Tolerance Tests on Relatives of Phenylketonuric Children[1]

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HSIA, DRISCOLL, TROLL AND KNOX (1956) reported that parents of phenylketonuric children showed an abnormal reaction to a test dose of l-phenylalanine. Serum phenylalanine concentrations in parents were elevated and remained high longer than in controls tested under the same conditions. While treating several phenylketonuric children with a low-phenylalanine diet, we had opportunity to test a group of parents and siblings to determine if they have a lessened ability to metabolize phenylalanine. Several parents of phenylketonuric children who were being treated at Muscatatuck State School, Butlerville, Indiana, were also tested. Paper chromatographic tests were used to simplify the analysis of blood and urine specimens. The test included determination of serum phenylalanine before and after ingestion of l-phenylalanine and examination of urine for the presence of phenylalanine derivatives which have been detected in urine of phenylketonurics, such as phenylpyruvic acid (Folling, 1934), phenylacetylglutamine (Woolf, 1951), and o-hydroxyphenylacetic acid (Boscott and Bickel, 1953; Armstrong, Shaw and Robinson, 1955).

MATERIALS AND METHODS

The subjects were ten parents and six siblings of phenylketonuric children and ten controls. Each set of parents was asked about consanguinity and none was reported. None of the controls were related. Parents B have two phenylketonuric and three normal children (Siblings B1, B2, B3); parents N have one phenylketonuric child and two normal children. Parents J have two phenylketonuric children. Parents M have one phenylketonuric child and parents D have one phenylketonuric and one normal child. The controls included eight research workers and residents at Children's Hospital (1–8), a three year old child (9), and the husband of a woman who had two phenylketonuric siblings (C10).

After an overnight fast each subject was given a test dose of l-phenylalanine, 0.1 g/kg body weight. Blood samples of one to five ml were collected before and one, two and four hours after ingestion of phenylalanine. A fasting urine sample was obtained, and urine was collected at intervals of one, two and four hours. Serum phenylalanine was determined using a paper chromatographic method (Berry, 1957). A small volume of blood serum was deproteinized using four volumes of 95 per cent ethanol. The alcoholic filtrate was used to prepare chromatograms. These were resolved in butanol-ethanol-water solvent (7–2–2) and developed with ninhydrin. Each urine specimen was analyzed for phenylalanine using paper chromatography

Received June 7, 1957.

[1] With partial support of USPHS, NIH Grant No. Ma-1175.

to determine the percentage of test dose excreted. Endogenous creatinine in urine was determined with the standard alkaline picric acid reagent. Creatinine ratios were used as a means of comparing isolated specimens independent of the 24-hour volume (Berry, Cain and Rogers, 1951). 2,4-Dinitrophenylhydrazine in alkaline solution was used to test for the presence of phenylpyruvic acid after concentration of the urine as suggested by Berry and Woolf (1949). A portion of each urine specimen was acidified to pH 1 and extracted twice with an equal volume of ether. The ether was evaporated and the residue taken up in 50 per cent ethanol using one-tenth the original volume. The presence of phenylpyruvic acid was confirmed using a paper chromatographic test sensitive to 1 μg phenylpyruvic acid/mg creatinine. An amount of the urine concentrate containing 200 μg and 500 μg of creatinine was used to prepare a chromatogram to be resolved in butanol-acetic acid-water (8-2-2). Phenylpyruvic acid after spraying with a freshly prepared solution of 5 per cent ferrous ammonium sulfate gave a green color which was stable on standing. The green color developed with the usual ferric chloride reagent was not stable on paper. o-Hydroxyphenylacetic acid was determined using the urine concentrate described above. An amount equivalent to 200 μg of creatinine was used for preparation of a chromatogram which was resolved in isopropanol-ammonia-water (8–1–1). o-Hydroxyphenylacetic acid was detected by spraying with diazotized sulfanilic acid. Approximately 50 per cent of the o-hydroxyphenylacetic acid was recovered with this simple procedure. (o-Hydroxyphenylacetic acid for use as a standard was kindly furnished by Dr. Marvin Armstrong, University of Utah Medical School, Salt Lake City, Utah.) Phenylacetylglutamine was separated from the urine remaining from the ether extraction by further extraction with ethyl acetate (Woolf, 1951). The extract was concentrated as described above. An amount equivalent to 200 μg of creatinine was used to prepare a chromatogram. Butanol-acetic acid-water was used as the solvent mixture. Phenylacetylglutamine appeared as a purple spot at Rf .90 after spraying the chromatogram with ninhydrin.

RESULTS

Results of phenylalanine tolerance tests are given in table 1. Among the controls, with one exception, control 8, the serum phenylalanine levels rose only 3 to 8 mg per cent above the fasting values within an hour after beginning the test. These were generally the highest levels reached, and the levels decreased thereafter. At the end of four hours they were 0 to 3 mg per cent above the initial values. With the exception noted for C8, the control values for serum phenylalanine were grouped fairly closely about the means of 7.4 mg per cent at one hour, 6.3 mg per cent at two hours, and 3.8 mg per cent at four hours after beginning of the test. The values for C8 were 11.2 mg per cent, 9.7 mg per cent, and 7.0 mg per cent at one, two and four hours, respectively. A phenylalanine tolerance curve was drawn for each individual by plotting serum phenylalanine concentration at each test period during the four hours. Each inch along the abscissa of the phenylalanine tolerance curve represented a phenylalanine concentration of 5 mg per cent, while each inch along the ordinate represented one hour. The area under each curve represented a summation of each person's tolerance of phenylalanine. These areas were measured with a Keuffel and

TABLE 1. RESULTS OF PHENYLALANINE TOLERANCE TESTS

	Sex	Serum Phenylalanine—mg%				Area Under Curve Sq. In.	Urinary Excretion of o-Hydroxyphenylacetic acid—µg/mg creatinine	
		Fast.	1 Hr.	2 Hrs.	4 Hrs.		2 Hrs.	4 Hrs.
Controls								
C1	F	2.2	8.0	7.3	4.9	4.9	—	—
C2	M	2.1	7.0	6.1	2.6	4.1	*	*
C3	F	1.9	6.9	7.0	5.0	4.7	—	—
C4	F	1.3	4.2	7.4	4.3	4.3	*	*
C5	M	1.1	5.2	5.6	1.8	3.2	—	—
C6	F	1.0	9.0	6.7	1.7	4.3	—	—
C7	F	1.5	9.7	6.4	4.4	4.9	1.5	—
C8	M	1.5	11.2	9.7	7.0	6.5	35.0	10.0
C9	F	2.5	5.5	3.7	2.2	2.7	—	—
C10	M	1.0	7.2	4.2	3.5	3.3	—	—
Mean		1.6	7.4	6.3	3.8	4.3		
Std. Dev.		.6	1.9	1.7	1.7	1.0		
Parents								
N	F	4.2	21.0	15.0	14.0	11.9	*	3.2
N	M	2.2	9.8	9.1	7.4	6.4	*	—
J	F	1.4	13.4	7.9	6.0	5.9	*	3.0
J	M	2.4	14.5	12.6	9.9	8.9	*	19.0
B	F	1.6	12.7	10.2	7.0	7.6	28.0	2.0
B	M	4.1	11.7	11.5	7.8	7.7	9.0	14.0
D	F	2.3	7.7	15.2	6.7	7.7	16.0	8.0
D	M	2.3	14.4	12.3	5.0	7.5	2.0	7.0
M	F	2.3	14.0	13.0	7.0	8.5	7.0	1.0
M	M	2.0	15.1	9.8	5.5	7.2	6.0	2.4
Mean		2.5	13.4	11.7	7.5	7.9	9.7	6.0
Std. Dev.		.9	3.5	2.4	2.7	1.7		
Siblings								
N1	M	2.8	9.0	19.0	7.1	9.2	*	2.0
N2	M	2.2	9.5	12.3	6.8	7.1	*	*
B1	M	2.2	11.2	9.0	6.8	6.5	9.0	32.0
B2	M	1.0	5.7	8.2	5.8	4.8	—	—
B3	M	2.3		6.6			—	—
D1	F	1.8	5.5	4.5	3.0	3.2	—	—

* Urine specimen was not obtained.

Esser planimeter and are given in table 1. The range of areas for controls was from 2.7 to 6.5 sq. in.; all but one, C8, were in the range of 2.7–4.9 sq. in.

Phenylalanine recovered in urine of controls ranged from 0.25 per cent to 1.12 per cent of the amount ingested. The average recovery was 0.68 per cent. None of the controls excreted phenylacetylglutamine in an amount that could be detected with the method described. Generally neither phenylpyruvic acid nor o-hydroxyphenylacetic acid was detected in any urine specimen from controls, although again C8 was exceptional. Both substances were found in urine of C8.

Parents of phenylketonuric children had fasting serum phenylalanine values in the same range as those found in the controls. However, one hour after taking l-phen-

ylalanine the levels in parents rose 5 to 17 mg per cent above the fasting values and decreased slightly thereafter. In one instance a peak of 13 mg per cent above the fasting level was reached two hours after beginning the test. Values for serum phenylalanine were still elevated 4 to 10 mg per cent above the fasting levels four hours after ingestion of l-phenylalanine. The mean values for parents of 13.4 mg per cent at one hour, 11.7 mg per cent at two hours and 7.5 mg per cent at four hours are approximately twice those for controls at the same times. Parent N♂ was somewhat exceptional among parents of phenylketonuric children in that his serum phenylalanine levels did not increase to the same extent. However, like the other parents, the phenylalanine level remained elevated after four hours. The range of areas under the phenylalanine tolerance curves for parents was from 5.9 to 11.9 sq. in., with a mean value of 7.9 sq. in. Using Fisher's "t" test (1950) a value of 5.97 was calculated for the difference between means of the areas under the curves of parent and control groups. The possibility that such difference would occur by chance is very small ($P < 0.0001$).

An average of 0.56 per cent of ingested phenylalanine was recovered in urine of parents, with a range from 0.24 to 1.49 per cent. Three of the parents, N♀, J♂, and J♀, excreted small amounts of phenylacetylglutamine. Excretion of this substance was not a consistent feature of the parents. Urine collected from parents between one and two hours or between one and four hours after ingestion of l-phenylalanine contained a small amount of o-hydroxyphenylacetic acid (see table 1). None was detected in fasting samples or in urine collected one hour after beginning the test. None of the parents excreted phenylpyruvic acid in amount which could be detected.

Three of the siblings, N1, N2, B1, were very similar to the group of parents. In each case serum phenylalanine levels rose to 7 to 9 mg per cent above fasting values within one hour after ingestion of phenylalanine. The levels remained high during the period of testing. These siblings, like their parents, excreted o-hydroxyphenylacetic acid in urine collected between one and four hours after beginning of the test. Sibling B1 excreted a small amount of phenylpyruvic acid and p-hydroxyphenyllactic acid. Siblings B2, B3, and D1 were similar to the control group. Phenylalanine levels were increased 3 to 4 mg per cent above the fasting values and decreased to 1 to 2 mg per cent above initial values within four hours. None of these siblings excreted o-hydroxyphenylacetic acid, phenylpyruvic acid or phenylacetylglutamine in an amount that could be detected.

DISCUSSION

In general our data on phenylalanine tolerance tests agree with those of Hsia and his associates. Their mean values for fasting samples are in the same range as the ones reported here. Mean values for serum phenylalanine at the one, two and four hour periods found by Hsia, et al, are higher by about 30 per cent than those observed by us. Both groups were relatively small, and phenylalanine determinations were by different methods. In both studies the values for serum phenylalanine four hours after ingestion of l-phenylalanine showed the greatest difference between parent and control groups. The amounts of phenylalanine recovered in the urine

during a four hour period in our study and a nine hour period in Hsia's did not appear to be of significance. The earlier study did not include examination of urine for phenylalanine derivatives.

The excretion of o-hydroxyphenylacetic acid, but not of phenylpyruvic acid, by the parents of phenylketonuric children needs further examination before a suitable explanation can be proposed. While the primary defect in phenylketonuria has not been definitely established, it has been thought that a deficiency of the enzyme responsible for conversion of phenylalanine to tyrosine results in accumulation of phenylpyruvic acid in blood and urine (Jervis, 1947). Other phenylalanine derivatives found in phenylketonuria are explained as the result of detoxification or oxidation of phenylpyruvic acid (Dalgliesh, 1954). Phenylpyruvic acid is not thought to be a normal intermediate in the metabolism of phenylalanine (Dalgliesh, 1955a). Armstrong and Shaw (1955) proposed the formation of an "activated phenylalanine" intermediate which in normal metabolism is converted principally to tyrosine, but which in phenylketonuria forms phenylpyruvic acid and other derivatives of phenylalanine. Dalgliesh (1955b) has shown that when the enzyme responsible for *para*-hydroxylation of phenylalanine is inactive or lacking, non-specific, less reactive enzymes act on phenylalanine to form *ortho*-hydroxy compounds.

Penrose (1935) and Jervis (1939) proposed that phenylketonuria is the manifestation of the action of a single recessive gene in the homozygous state. Hsia, et al, reported that the heterozygote could be detected by the use of phenylalanine tolerance tests. Our results indicate also that parents of phenylketonuric children have more elevated serum phenylalanine levels after ingestion of l-phenylalanine than do controls and that the elevation persists longer in the parents. If we assume that this difference after phenylalanine tolerance testing is the result of the heterozygous condition, then the similarity of control 8 to parents of phenylketonuric children would indicate that he is a carrier of the recessive gene. While the group means for serum phenylalanine were different at each test period, the ranges of values for parent and control groups overlapped. If C8 is omitted from the control group, the corrected means are 7.9 ± 1.6, 6.0 ± 1.3, 3.4 ± 1.3 mg per cent at one, two and four hours. The corrected mean area under the phenylalanine tolerance curves for controls is 4.1 ± 0.8 sq. in. compared with 7.9 ± 1.7 sq. in. for parents. If determination of serum phenylalanine levels one, two and four hours after ingestion of l-phenylalanine is combined with examination of urine for o-hydroxyphenylacetic acid, the classification of a given individual as normal or carrier may be possible. However, many more tests on both parents and controls are needed to determine the probable error of such classification. The carrier incidence is thought to be between 1 in 100 and 1 in 200 (Jervis, 1939; Cawte, 1954). One individual in the control group of 19 reported by Hsia, et al, and presumably one in the present control group of ten could be classified as carriers. This may be coincidence, or the carrier incidence may be higher than supposed.

If the carrier state for such a defect as phenylketonuria can be detected, the procedure described may become of importance in genetic counseling. Control 10, for example, appears to have normal phenylalanine metabolism. Serum phenylalanine levels following ingestion of l-phenylalanine were only slightly elevated; the area

under his phenylalanine tolerance curve was 3.3 sq. in., a value lower than the mean for the control group. No o-hydroxyphenylacetic acid was detected in urine. If we assume that phenylketonuria results only from the homozygous recessive condition, children of C10 should be normal, even though his wife, who had two phenylketonuric siblings, might carry the recessive gene.

An interesting application of the phenylalanine tolerance test arose with a five year old mentally retarded child. A diagnosis of phenylketonuria had been made on the basis of a few positive ferric chloride tests for phenylpyruvic acid in urine, although most urine specimens were negative. She was placed on a phenylalanine-low diet and showed little or no response. She was given l-phenylalanine and serum was collected at intervals as described. The fasting level was 1.8 mg per cent; at one hour, 6.0 mg per cent; at two hours, 8.7 mg per cent; and at four hours, 1.9 mg per cent. Urine specimens obtained at the same time as blood were negative for phenylpyruvic acid. This seems to indicate that the child is not a phenylketonuric.

SUMMARY

A phenylalanine tolerance test was given to ten parents of patients with phenylketonuria. The phenylalanine levels in blood serum were determined by paper chromatography one, two and four hours subsequent to beginning the test. Urine specimens collected at the same times were analyzed for phenylalanine and its derivatives. The same test was given to six siblings and to ten controls. In general the serum phenylalanine value in parents rose to levels approximately twice those found in the controls. Three siblings were similar to their parents, and three were similar to the controls. One control was very similar to parents. o-Hydroxyphenylacetic acid was excreted by the parents, by the siblings who had elevated serum phenylalanine levels, and by the one control who had relatively high serum phenylalanine values.

ACKNOWLEDGMENT

The authors wish to express their appreciation to the parents and siblings of phenylketonuric children and to residents and research workers at Children's Hospital who participated in the phenylalanine tolerance tests. We also wish to thank Dr. Hans Meyer, Muscatatuck State School, Butlerville, Indiana, for referring parents to us. We express our appreciation to Dr. Josef Warkany for his valuable comments and encouragement during preparation of this paper.

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Frequency of Multiple Birth in Three Cities of Japan*

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INTRODUCTION

SINCE genetic studies on human traits by the twin method require unbiased samples of monozygotic (MZ) and dizygotic (DZ) twins, it is important to know the frequency of twin births and the ratio of MZ twins to DZ twins in the general population. Komai and Fukuoka (1936) estimated the frequency of twin births from information submitted by midwives. The authors found a lower frequency of DZ twins and roughly the same frequency of MZ twins among Japanese as among Caucasians and Negroes. Midwives' information is, however, not reliable in some respects, in addition, there are still many deliveries not attended by midwives and the opportunity being admitted into obstetric hospitals is increasing. In both cases the deliveries are not reported by midwives.

Since 1948 live birth and stillbirth registrations at health centers have been required by law to note whether the birth or stillbirth is single or multiple. These registrations are no doubt the most unbiased source of information available at the present time on the frequency of multiple births. The following data was obtained by a survey of the birth registrations in three cities.

METHODS

Records of live birth and stillbirth registrations by the inhabitants in Sapporo City (population about 340,000), Nakano District of Tokyo (population about 200,000–270,000) and Nada District of Kobe City (population about 110,000–130,000) were examined. Only the registrations for children both of whose parents were Japanese were included. If at least one member of twins or triplets was stillborn, the pair or the set was classified as stillbirth. The data for births occurring during the five years period 1949 through 1953 were examined.

RESULTS

The frequency of single and multiple births is shown in table 1. The frequencies of twins among live born infants as well as that among the total of all births do not vary significantly among the three districts ($\chi^2_{(2)} = 0.37$, $0.90 > P > 0.80$ and $\chi^2_{(2)} = 1.85$, $0.50 > P > 0.30$). However, significant inter-district differences were found when the frequencies of twins among stillborn infants were compared ($\chi^2_{(2)} = 13.91$, $0.001 > P$).

* This report was previously published in a book "Soseiji no Kenkyu, Vol. II" in Japanese. The study was financially supported by Grants for Scientific Research of Ministry of Education.

Received April 6, 1957.

TABLE 1. LIVE BIRTH AND STILLBIRTH FREQUENCIES IN THREE CITY DISTRICTS OF JAPAN (1949–1953)

District		Single		Twins		Triplets		Total
		No.	%	No.**	%	No.**	%	No.**
Sapporo	L	41,328	99.53	196	0.47	0	0	41,524
	S	6,996	98.73	89	1.26	1	0.01	7,086
	L + S	48,324	99.41	285	0.59	1	0.00	48,610
Nakano	L	20,084	99.50	100	0.50	0	0	20,184
Tokyo	S	1,941	97.49	48	2.41	2	0.10	1,991
	L + S	22,025	99.32	149*	0.67	2	0.01	22,176*
Nada	L	12,000	99.55	54	0.45	0	0	12,054
Kobe	S	1,757	98.21	32	1.79	0	0	1,789
	L + S	13,757	99.38	86	0.62	0	0	13,843
Total	L	73,412	99.53	350	0.47	0	0	73,762
	S	10,694	98.42	169	1.56	3	0.03	10,866
	L + S	84,106	99.38	520*	0.61	3	0.00	84,629*

L = live birth.
S = stillbirth.
* including one twin pair, one of which is live born and it is not known whether the other is live- or stillborn.
** indicating the numbers of deliveries, not the numbers of children.

TABLE 2. SEX OF TWIN PAIRS, THE ESTIMATED FREQUENCY OF EACH ZYGOSITY, AND THE RATIO OF MZ TO DZ BY WEINBERG'S METHOD

District		Observed No. of Pairs			Estimated (Weinberg's Method)				
		♂♂	♂♀	♀♀	MZ		DZ		$\frac{MZ}{DZ}$
					No.	%	No.	%	
Sapporo	L	84	36	76	124	0.30	72	0.17	1.72
	S	39	19	31	51	0.70	38	0.53	1.34
	L + S	123	55	107	175	0.36	110	0.22	1.54
Nakano	L	30	9	34	55	0.37	18	0.12	3.05
Tokyo	S	14	9	20	25	1.42	18	1.02	1.39
	L + S	44	18	54	80	0.46	36	0.21	2.22
Nada	L	22	12	20	30	0.25	24	0.20	1.25
Kobe	S	11	7	14	18	1.00	14	0.78	1.28
	L + S	33	19	34	48	0.38	38	0.25	1.26
Total	L	136	57	130	209	0.31	114	0.17	1.83
	S	64	35	65	94	0.89	70	0.67	1.34
	L + S	200	92	195	303	0.38	184	0.23	1.65
Osaka (Komai et al., 1936)		1688	1017	1459	2130	0.29	2034	0.27	1.05

L = live birth.
S = stillbirth.

Table 2 shows the sex of the members of twin pairs, the frequency of each type of twin pair and the ratio of MZ twins to DZ twins as estimated by Weinberg's method. Twin pairs in which the sex of one or both twins was unknown, were omitted. The ratio of same-sexed pairs to opposite-sexed pairs among live births and among stillbirths as well as among the total of all births does not differ significantly among the three districts ($\chi^2_{(2)} = 2.268$, $0.50 > P > 0.30$, $\chi^2_{(2)} = 0.00953$, $P > 0.99$ and $\chi^2_{(2)} = 1.468$, $0.50 > P > 0.30$ respectively).

There were three cases of triplets. In all cases at least one member of the set was stillborn. The frequency coincides with that estimated from twin frequency by Hellin's law (Fisher's $P = 0.696$ for the stillbirth and Fisher's $P = 0.625$ for all births). There was no record of quadruplet birth or greater multiple birth.

DISCUSSION

The inter-district differences of twin frequency among stillborn infants were significant. These differences are possibly correlated with the rate of stillbirth (stillbirth/stillbirth + live birth) among single birth, because the rates differ significantly among three districts ($\chi^2_{(2)} = 437.5$, $0.001 > P$). Among twin birth itself the rates of stillbirth do not differ significantly among three districts ($\chi^2_{(2)} = 1.09$, $0.50 > P > 0.30$). This finding suggests in agreement with other evidence that the causes of stillbirth in twins are not identical with those in single births, and that the frequency of twins may be affected by the rate of stillbirths among single born subjects.

According to Neel and Schull (1956) the stillbirth rate in Hiroshima and Nagasaki is 1.40 per cent. The rates in the present survey are 14.48 per cent (Sapporo), 8.81 per cent (Nakano of Tokyo) and 12.77 per cent (Nada of Kobe). All figures are much higher than those reported by Neel and Schull. Under present Japanese law stillbirth registrations need not to be made until one week after delivery, and some neonatal deaths prior to one week of age may be reported as "stillbirth". The rate of neonatal deaths during the first six day postpartum reported by Neel and Schull is 1.43 per cent, hence the rate of early deaths including both of stillbirths and early neonatal deaths in Hiroshima and Nagasaki becomes 2.79 per cent. This rate is still far under the "stillbirth" rate of this survey. The recent statistics published by The Institute of Population Problems of the Welfare Ministry (1954) shows that the stillbirth rate, which probably includes some neonatal deaths, is increasing rapidly after World War II. Simultaneously the rate of reported induced abortions performed after the fourth month of pregnancy is increasing. According to the same statistics the average "stillbirth" rate during the period 1949 through 1953 is 7.99 per cent. The high "stillbirth" rate and its heterogeneity in this survey can be explained partly by including some neonatal deaths, partly by artificial abortions.

To answer the question whether Weinberg's method should be corrected for the deviation of the sex-ratio from one, the following data are available. There were 37,645 males and 35,767 females among the 73,762 live births of known sex in the three districts. From this figure the ratio of same-sexed DZ twins to opposite-sexed DZ twins is expected to be 1.0011. The correction for the excess of males is unimportant, since the total number of twin pairs in this survey is around 500.

As shown in table 2, the obtained results show a higher frequency of MZ twins

and lower frequency of DZ twins than the figures for Osaka City reported by Komai and Fukuoka. The present data, however, are in agreement with their finding of a lower frequency of DZ twins and approximately the same frequency of MZ twins among the Japanese as among Caucasians and Negroes.

SUMMARY

The frequency of twin births, among all births, in three city districts in Japan is 0.61 per cent. The ratio of monozygotic twins to dizygotic twins is estimated as 1.65:1. The stillbirth rate was found to be much greater than that reported for the populations of Hiroshima and Nagasaki. The origin of this high rate was discussed, and it was suspected that some neonatal deaths were reported as stillbirths.

ACKNOWLEDGMENTS

This study is a part of a joint study on twins carried out by The Twin Research Group, and the author wishes to thank the members and associates of the group, Drs. E. Matsunaga and M. Takagi, who carried out the survey in Sapporo City and Kobe City, Dr. H. Kamide, Miss K. Ikeda, Miss T. Koide, Mr. K. Yoshihawa and others for their assistance.

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Selective Survival in Dizygotic Twins in Relation to the ABO Blood Groups*

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SELECTIVE PROCESSES affecting fetal survival have important implications for human genetics, and have a particular bearing upon the interpretation of twin evidence. It is the possible importance of early selection in dizygotic twins in relation to the ABO blood groups which constitutes the subject of this paper.

An early observation on the fetal development of twins, which has been the subject of constant review and reinterpretation, concerns the fusion of twin placentae, and the consequent occurrence of vascular communications between the placentae. It was originally held that a fused or single placenta, and a single chorion, were both indisputable evidence, and a prerequisite for proof of monozygotic twinning in all placental mammals from armadillo to man. It is now known that at least one third of all human monozygotic twins may have separate chorions as well as separate placentae (Essen-Moller 1941, Corner 1955). While a single chorion is not known to occur in dizygotic twinning, except secondarily, as a result of fusion and partial absorption, (Arey 1922), a single placenta may be found. In dizygotic twin cattle it has long been known that fusion of the placentae may be accompanied by vascular communications between the placental vessels of the twin fetuses. In 1916 Lillie explained the 'free-martin' in dizygotic cattle twinning on the basis of fusion and vascular communication between placentae; in 1945 Owen described the 'red-blood-cell chimera' in dizygotic cattle twins, as a result of this same phenomenon. In spite of these findings, it was generally considered that in man actual vascular communications between the placentae occurred only in monozygotic twins, (Price 1950, Wenner 1952), until Dunsford, et al, in 1953, discovered the first red-blood-cell chimera in a human twin. This discovery suggested that vascular communications between placentae, not only can, but do occur in human dizygotic twins. It has recently been confirmed (Booth, et al 1957; Nicholas, et al 1957). Because of the common occurrence of red-blood-cell chimeras in dizygotic cattle twins, and their apparent rarity in human twins, it is now assumed that vascular communications between human dizygotic twin placentae is a rare event. However, with the placental, developmental, and serological differences which exist between man and cattle (Hancock 1954), there is no reason for assuming that the consequences of this event would be entirely comparable in man and cattle. It is possible that in man the more common consequence might be early fetal death rather than the occurrence of a blood group chimera.

In man, a possible relationship between early fetal death and the blood group

* Prepared from a paper given at the Ninth Annual Meeting, American Society of Human Genetics, Storrs, Connecticut, August 30, 1956.

Received July 10, 1957.

factors has been frequently suggested. With discovery of the role of maternal-fetal Rh incompatibility in the pathogenesis of erythroblastosis (Levine, Katzin and Burnham 1941), an extensive literature has developed, indicating that maternal-fetal blood incompatibility in the ABO system may be a cause of sterility or early fetal death, (Levine 1943; Fisher, as quoted by Race and Sanger 1950). That fetal death due to incompatibility could occur in very early development is known, for the AB agglutinogens are present in detectable strength in the red blood cells of the month old fetus (Kemp 1930; Wiener 1943). It is therefore possible that an exchange of incompatible blood between twin fetuses, as well as maternal-fetal exchange, could result in fetal death and abortion well before the end of the third month of development. There is little likelihood that a pregnancy terminated before this time would be recorded in the obstetrical record as having been that of a multiple conception. Even if but one of the twin fetuses was to die prior to this time, as a result of either maternal, or co-twin blood incompatibility, and the pregnancy continued to term, absorption of one twin fetus might easily obscure the original twin status of the surviving infant (Kindred 1944). The assumed frequency of multiple ovulation in the human female, and consequently of multiple conception, is based in large part upon the observed frequency of dizygotic twinning. Obviously then, a selective survival for dizygotic twins taking place within the first two, or even three, months of fetal life might not be revealed by data commonly available in the obstetrical record. If an appreciable early loss of the products of multiple ovulation is in fact occurring, this would have important implications, not only for our theories concerning human twinning and the methods employed in twin analysis, but would also add to our understanding of human ovulation and human fertility as well.

If an early loss of dizygotic twins is occurring due to ABO incompatibility, it should be found that dizygotic twins differ less in their blood group factors than would otherwise be expected. This hypothesis can be tested by comparing the intrapair blood group differences of dizygotic twins with those of single born siblings, or by calculating the theoretical expectancies, utilizing population gene frequencies. Schiff and von Verschuer (1933) in utilizing the twin study method for verifying the inheritance of the ABO blood group system noted that the number of dizygotic twin pairs discordant in the ABO system was less than expected. A similar observation has been reported by Gedda (1951). Beginning in 1954, a serological study of twins and their available siblings was undertaken specifically to test the hypothesis of early fetal death in dizygotic twins as a result of blood incompatibility.

THE STUDY SAMPLE

The first prerequisite for a study of blood group factors in relation to survival in twins is to obtain a sample of twin subjects and their siblings unselected on the basis of any prior knowledge as to their blood group differences. The subjects obtained for this study came from two different sources, unselected as to their zygosity, and free from any discernible bias as to their blood group factors. The larger of the two groups of twins, which will be referred to as the adult series, are twin pairs and their

available siblings who have been under extensive study for several years (Osborne 1956), and will be reported in greater detail elsewhere. This series consists of 131 pairs of Caucasian twins drawn from a variety of sources in New York City, unselected as to sex and zygosity, ranging in age from 18 to 55 years, and obtained for the purpose of establishing a population of adult twin subjects in good general health. Twenty-nine siblings were available and willing to participate in the study, and have received examinations comparable to those given the twin propositi.

The second group of twins, which will be referred to as the juvenile series, consists of all the twins available for study at the ages of 4 to 8 years who were born in Sloane Hospital between 1946 and 1952, to women included in a large cooperative study, known as the Fetal Life Study, carried out under the Departments of Obstetrics and Pediatrics (McIntosh et al 1954). In this cooperative study, all of the expectant mothers admitted to Sloane Antepartum Clinic with a duration of pregnancy of four months or less, on their first visit, were included in the study. After exclusion of the women transferred or discharged from the clinic for various reasons, (McIntosh, et al 1954), there were a total of 5964 pregnancies, of which 84 were twin pregnancies. In 1955, the parents of twins in this population were contacted by the original study group, and all of the pairs with both members still surviving and available for study, were brought into the pediatric clinic for blood tests and zygosity diagnosis. A total of 100 twins, of which there were 48 complete pairs and 18 single born siblings were studied for this population. No selection factor which would bias this sample could be detected for the twins who had either left the hospital area, or failed to respond for this study. It is therefore considered that this juvenile series constitutes as unbiased and complete an ascertainment of twins from an essentially normal reproductive population as it is possible to obtain for the purposes of the present investigation.

A total of 179 twin pairs were obtained from these two samples, of which 94 pairs are dizygotic: 60 pairs in the adult series, and 34 pairs in the juvenile series. 47 single born sibs of the twins were also studied: 29 in the adult series, and 18 in the juvenile series.

The blood determinations, for both the adult and juvenile series, were done by professional blood laboratories; all determinations were done at least in duplicate and independently, to assure the highest degree of typing accuracy practicable. The diagnosis of zygosity in all of the like sex twins has been based upon proving dizygosity, first, by a proven difference in a blood group factor, and then by adding other reliable criteria such as eye color, hair color, ear form, and digital hair; only accepting differences which left no question as to the diagnosis of dizygosity. These criteria, as well as the method of diagnosis, have been discussed (Osborne 1956), and will be presented in detail in a forthcoming publication. The advantage of this method of diagnosis, in general, and particularly in the present study, is that it provides a strict test of the hypothesis, with a known direction of possible error in diagnosis. The only mistake in diagnosis which can occur with this method, is the misclassification of an unusually similar pair of dizygotic twins as monozygotic. By placing the first emphasis in the diagnosis upon a proven difference in a blood factor, it is possible that some bias has been introduced for the purposes of the present

study. This bias, however, would tend to increase, rather than decrease, the average intra-pair difference in the dizygotic twins for their blood group factors, and would make the test of the present hypothesis a more conservative one.

RESULTS

In table 1 the dizygotic twin pairs are listed separately for the adult and juvenile series, according to the ABO blood types. The male and female like-sexed pairs have been combined, as there were no apparent sex differences in either series. In the adult dizygotic twins 70.0 per cent were found to be concordant in their ABO blood types, and in the juveniles 91.3 per cent are concordant.

The number of concordant twin pairs that would be expected to occur in these two populations are compared to the observed in table 2. The juvenile series is a racially mixed population, (white and negro), consequently, it has been necessary to handle the white and negro twin pairs separately. Because of the obvious difference between the juvenile and adult series in age, as well as in the per cent concordant for the ABO system as seen in table 1, the juvenile whites have not been combined with the white adult series. The gene frequencies used for calculating the expected

TABLE 1. ABO BLOOD GROUPS OF DIZYGOTIC TWIN PAIRS

	Adult		Total		Juvenile		Total	
	Like Sex	Unlike Sex	n	%	Like Sex	Unlike Sex	n	%
O-O	13	8	21	35.0	13 (8)*	9 (6)	22	64.8
A-A	11	3	14	23.3	1 (1)	6 (2)	7	20.7
B-B	2	0	2	3.4	1 (1)	0	1	2.9
AB-AB	4	1	5	8.3	1	0	1	2.9
Concordant	30	12	42	70.0	16	15	31	91.3
O-A	7	1	8	13.3	1 (1)	0	1	2.9
O-B	2	3	5	8.3	0	1 (1)	1	2.9
O-AB	0	1	1	1.7	0	0	0	0
A-B	3	0	3	5.0	0	0	0	0
A-AB	0	1	1	1.7	0	0	0	0
B-AB	0	0	0	0	0	1	1	2.9
Discordant	12	6	18	30.0	1	2	3	8.7
Total	42	18	60		17	17	34	

* Numbers in parenthesis designate the number of negro twin pairs out of the Total Juvenile series in the particular category.

TABLE 2. DIZYGOTIC TWIN PAIRS CONCORDANT FOR ABO

	N	Observed	Expected	Variance	χ^2	P
Juvenile White	14	13	9.093	3.187	4.790*	.03
Juvenile Negro	20	18	12.328	4.729	6.803*	.01
Adult	60	42	38.970	13.659	1.659	.20

* With one degree of freedom.

TABLE 3. ABO CONCORDANCIES AND DISCORDANCIES AMONG SIB-SIB AND TWIN-SIB PAIRINGS

	MZ				DZ				
	Sib-Sib		MZ-Sib		Sib-Sib		DZ-Sib		
	Conc.	Disc.	Conc.	Disc.	Conc.	Disc.	Conc.	Disc.	Total
Adult	8	10	8	7	3	4	11	4	55
Juvenile White	3	0	0	3	0	0	2	0	8
Juvenile Negro	0	0	0	0	4	4	6	4	12
Total	11	10	8	10	7	8	19	8	75
Per Cent	52.4		44.4		46.7		70.4		

proportion of discordant negro twin pairs are the New York City figures of Landsteiner and Levine (Moore 1955). The phenotype frequencies given by Landsteiner and Levine agree very closely with those of the study population; since the calculated gene frequencies would be more reliable from the larger data, these were used, ($p = .198$, $q = .142$, $r = .660$). The gene frequencies used for whites are the combined New York City and North Carolina frequencies of Landsteiner, Levine, Weiner, and Boyd, ($p = .248$, $q = .078$, $r = .674$), as given by Moore (1955). These frequencies appeared to fit the white data of this study. Using these gene frequencies, the probabilities of different mating types were calculated, and the resulting probability that both members of a dizygotic twin pair would be concordant in their ABO blood groups was obtained. From this the expected number of concordant twin pairs was calculated for comparison to the observed as presented in table 2. Chi-square was calculated by treating the twin pairs as families of two,

$$\chi^2 = (\text{observed} - \text{expected})^2/\text{variance}. \qquad \text{(Smith 1956)}.$$

The variance is $(c \times n)(1 - c)$, where c equals the probability of concordant twin pairs, and n is the total number of dizygotic pairs. The excess of concordant pairs in the juvenile white has a probability value of 0.03, and in the juvenile negro it is less than 0.01, while for the adult series the excess of concordant pairs is not statistically significant. In the negroes it is primarily type O concordant pairs which contribute to the observed excess. If the type O pairs are taken separately, by the same method as above, $\chi^2 = 15.280$, $P = <.001$. In the juvenile white it is similarly the Type O pairs which contribute the most to the concordancy excess. In the adults it is again an excess of type O, with a relatively great excess of AB–AB pairs, and an actual deficiency of A–A and B–B pairs.

The significant excess of dizygotic pairs concordant for ABO blood groups among both the white and negro juvenile twins, plus the excess of concordant pairs in the adult series, even though not significant in the latter, strongly support a hypothesis of selective survival in dizygotic twins in relation to the ABO system. The similarity in the concordancy pattern between the adult and juvenile series, in the presence of the marked difference of concordancy ratio in the two series, suggests that some factors other than the ABO blood groups alone may be associated with survival in dizygotic twins. Aside from age, which by definition separate the adult and juvenile series, there are important factors peculiar to each group which will be discussed presently.

The concordance-discordance data for the sibling pairs are presented in table 3. While the number of sibling pairs are not adequate for statistical treatment, they are presented here as they lend some support to certain other observations and should be of interest for comparison with the data of other studies. The sibling pairs of the monozygotic and dizygotic twins are presented separately. Sibling pairs were obtained by pairing the single born sibs of the twin propositi. If there was only one single born sibling of a twin pair, obviously no sibling (sib-sib) pair could be formed, but this sib is paired with one of his twin born sibs to form a MZ–Sib, or DZ–Sib pair, as the case may be. Two single born siblings of a twin pair provided one Sib–Sib pair, and two MZ–Sib or DZ–Sib pairings, only one member of a twin pair taken at random being used for such pairings. The monozygotic Sib–Sib, MZ–Sib and dizygotic Sib–Sib pairings very nearly agree in the percent of concordant pairs, while the proportion of concordant pairs in the DZ–Sib comparison is much higher, closely resembling the value observed for dizygotic twin pairs. The high DZ–Sib concordancy ratio, and its similarity to the dizygotic twin pair value, rather than to the other sib comparisons, would seem to suggest that some factor other than vascular communications between the twin placentae may be responsible for the excessive dizygotic twin concordancies.

DISCUSSION

In 1933 Schiff and Von Verschuer reported a study of 446 twin pairs, 202 monozygotic, and 244 dizygotic, for whom they obtained ABO blood groups. These authors noted a deficiency of like sex dizygotics and of unlike sex twin pairs discordant for the ABO blood groups. Of the 244 dizygotic pairs, 156 or 63.9 per cent were found to be concordant for ABO. According to their calculations, the theoretical expectancy was only 45.6 per cent (Schiff and Von Verschuer 1933). Their theoretical value was apparently obtained empirically, and while it agrees exactly with the observed value for sibling pairs in the present data, this theoretical value is less than would be calculated from German gene frequencies using the methods of the present study. Gedda (1951) reported findings similar to those of Schiff and Von Verschuer and those of the current study. In 39 pairs of dizygotic twins, 64 per cent were found to be concordant in their ABO types, while only 58 per cent of 93 sib pairs were concordant. The blood group combinations in Gedda's data are not available, but Schiff and Verschuer's data show, as in the present study, that the twins concordant for Type O account for most of the observed excess of concordant pairs. The similarity of the findings of the present study with those of the two earlier studies could well be fortuitous, but it must be considered to give added support to a hypothesis of selective survival. The fact that other reports of this nature are lacking is not surprising, for the blood grouping of large numbers of twins has been almost exclusively done for the sole purpose of diagnosing zygosity. In such studies unlike sex pairs are not blood grouped and the statistical treatment of the blood data is initially based upon an assumption that no selective factor will interfere with realization of the mathematically expected segregation ratios. That selective survival in dizygotic twins may be taking place, in relation to the ABO blood groups, would now be difficult to question, particularly in the light of the significant excess of concordant pairs

in both the white and negro juveniles who represent unbiased twin samples of a normal reproductive population. The relative excess of concordant pairs in the juvenile as compared to the adult series, however, suggests something other than a simple blood incompatibility factor, and may actually provide an opportunity for investigating other factors which may be associated with selective survival in relation to the blood groups.

Important differences exist between the adult and juvenile twin series which may have an important bearing upon the comparative findings in the two populations. In the adult series it was not only necessary for both members of every twin pair to survive into adult life, instead of only to the age of 4 to 8 years, but it was also necessary for both members of each adult pair to present a reasonable state of health to be considered eligible for study. For the juvenile series, on the other hand, survival and availability until the age of 4 to 8 years were the sole selection criteria. If severely impaired health at an early age is positively correlated with adult health, which would appear to be a reasonable assumption, many of the juvenile twins would fail to qualify as adults for the adult twin study population. The medical histories of the juvenile twins were independently evaluated by the authors, and a conservative count was made of the twins definitely presenting a sufficient impairment of health to preclude their possible consideration, even at their present age, for a study comparable to the adult series. [Examples of twin members considered to be in poor health are: 1. a Mongolian Idiot; 2. a celiac, requiring constant medical care, for Acute U.R.I. conditions, (including: bilateral otitis media, bronchitis, spasmodic croup, tonsilitis, and pharyngitis)—from 9 mos. of age until the time studied at 4.8 yrs.; 3. a child with a systolic murmur detectable at 5 wks. of age and persisting to the present, cerebral palsy spastic diplegia, and having autistic behavior; 4. a child having episodes of seizures and convulsions from 2 mos. of age to the present, mentally retarded, and having poor motor coordination.] On the basis of the medical record thirty per cent of the juvenile twin pairs studied (40 per cent of the negro, and 50 per cent of the white), were considered unsuited for a study comparable to that of the adult group. Most interestingly, these pairs in inferior health included one male and one female monozygotic pair, one male and one female like sex dizygotic twin pair, and 11 out of the total of 17 unlike sex pairs in this population. In the unstudied pairs, 28.6 per cent were similarly classified as being in poor health. It is apparent that the adult twin series, and perhaps the dizygotics in particular, represent pairs selected by health, and survival, from a vastly larger initial twin population than the juvenile series. If health and survival correlate with favorableness of prenatal development, and if it can be further assumed that unfavorable prenatal development is associated with conditions which increase the likelihood of either inter-twin or maternal-fetal blood exchange, then it would be expected that twins selected for good health, in this case the adult twins, would have a relatively larger proportion of pairs discordant for their blood factors. The possible importance of this selection factor in the present study may be supported by the suggestive findings of Bennett and Walker (1956). In studying fertility and the blood groups in East Anglian blood donors, it was found that for the newly born child, the chance of death under 10 years of age was significantly greater ($\chi^2 = 10.4$, $P = 0.001$) when the father is of

group O, Rh positive. In populations where approximately one half of the fathers would be of type O, 85 per cent of which would be Rh positive, a larger proportion of the type O concordant dizygotic twin pairs would be expected to have type O, Rh positive fathers. The present data indicated that concordant pairs, particularly if they are concordant for type O, are favoured presumably in prenatal life. If there were a differential loss of type O twins in the first 10 years of life, then by adult life, the initial excess of type O concordant pairs would be in part lost, resulting, as we have observed, in the relatively smaller proportions of concordant pairs in the adult series.

A second difference between the adult and juvenile twin series concerns that of twin birth rank. In the adult series 36.7 per cent of the dizygotic twins were the result of the first pregnancy, while for the juvenile series only 23.5 per cent represented the first pregnancy. The same relative proportions hold for the monozygotic twin pairs, being 40.9 per cent and 21.4 per cent respectively. These differences in parity between the two twin samples, while not statistically significant, suggest a difference in reproductive history, and the observed differences in the proportion of twin pairs concordant for the ABO blood groups may reflect a prenatal affect associated with maternal age and parity. A differential fertility with maternal age and the ABO blood groups has been shown by Kirk, Kirk, and Stenhouse (1953) with the fertility of type O women increasing at the age of the highest frequency of dizygotic twinning. It may well be that there is an excess of type O women having dizygotic twins which could in part account for the observed excess of type O concordant twin pairs. If maternal and parity factors relate to both the ABO blood groups and to dizygotic twinning then in twin populations characterized by different parity orders contrasting concordancy ratios could attain, as has been observed in the present study. Certainly the possibility of a maternal and parity affect is suggested; this is presently under investigation by the authors.

There would appear to be little doubt but that in certain types of twin populations, at least, some selective factors may be operating to significantly alter the theoretically expected segregation ratios in the ABO blood group system. Whether this is due to early fetal death as a result of a transplacental exchange of incompatible blood, or vascular communications between dizygotic twin placentae can not be determined. Mechanisms other than antigenic incompatibility, such as dispermic fertilization of a single ovum, could also result in similar findings. However, since there is no evidence at the present time for such twinning mechanisms, and since antigenic incompatibility has been established as a factor in fetal survival, this constitutes the more likely hypothesis. Until such time as this problem can be more fully evaluated, the present findings clearly imply the necessity for caution in employing calculated probabilities for a correct diagnosis of zygosity. Perhaps most importantly, the present study brings twin evidence to the support of the hypothesis of a relationship between the ABO blood group system, fertility, and early fetal death, with the implication that the phenomenon of multiple ovulation and conception is more frequent than has been suspected, and may consequently be intimately associated with the general problem of human fertility.

SUMMARY

Evidence has been presented which supports a hypothesis for a selective survival in dizygotic twins in relation to the ABO blood group system, by demonstrating an excess of dizygotic twin pairs concordant in the ABO blood groups. The possible association of this selective mechanism to maternal age and parity are discussed, and some of its implications are presented.

ACKNOWLEDGMENTS

Personal acknowledgment is given to Dr. L. C. Dunn and Dr. Howard Levene for reading the manuscript, and again to Dr. Levene for his statistical counsel. Special thanks to Miss Helen Williams and Mrs. Eleanor Fries for their valuable assistance in obtaining the juvenile series, and to Dr. Amos Cahan and Mr. James Jack of the Knickerbocker Foundation Inc., Dr. John Scudder and Miss Mary Sargent, together with the staff of the Presbyterian Hospital Blood Bank, and Dr. Philip Levine of the Ortho Research Foundation for the blood determinations.

The juvenile series was obtained from a study conducted in the Department of Pediatrics, Columbia University, College of Physicians & Surgeons, and Babies Hospital, a study aided by grants from the Rockefeller Foundation, the Life Insurance Medical Research Fund, the New York State Department of Health, the New York Foundation, The Association for the Aid of Crippled Children, and the U. S. Public Health Service (Grant G-4194).

The present investigation, the collection of the adult series, as well as all of the blood data in this study, was made possible by the support of The Commonwealth Fund within the facilities of the Presbyterian Hospital Blood Bank, and the Department of Medicine, Columbia University, College of Physicians & Surgeons and the Department of Pediatrics in Vanderbilt Clinic.

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BOOK REVIEWS

Developmental Abnormalities of the Eye

By IDA MANN, Philadelphia: J. B. Lippincott Co., 1957. Second Edition. 419 + xi pages. $15.00.

THE SPLENDID first edition of this work appeared twenty years ago. One might expect this "revised and enlarged" edition to be more different than it is. The bibliography has grown from 500 items to 598, but the book is not commensurately larger. There are actually 25 fewer pages, owing to the use of a larger type-page. There has been hardly any real revision, but mostly insertions of new paragraphs and the modernization of a few terms. The number of illustrations has not been increased, and only a very few of the old ones have been replaced or modified. The fact that the first edition was long out of print was reason enough for the bringing out of the second, even with no changes at all. These remarks are not intended as criticism of it, but only to inform those who own the first edition that they need not think that they must buy the second, sight unseen, and would then want to throw away the first.

In her introductory chapter Miss Mann now concedes that dietary manipulation of mothers can generate anomalies in offspring, but she might have given much more new information about the passage of substances through the placenta. The coverage of experimental embryology has not been updated, and while the discussion of genetics has been partly rewritten it has scarcely been improved.

Mandibulo-facial dyostosis and gargoylism have been given place in Chap. II (on the skull); and in Chap. III (the eye as a whole), buphthalmia and adult glaucoma simplex have gotten genetically dissociated.

In Chaps. IV and V (fundus oculi) practically all of the conditions dealt with are hereditary, but Leber's optic atrophy is still left "sex-linked," the classification of albinisms has not been modernized, and the slightly altered treatment of the color-blindnesses remains about as bad as it could be. Miss Mann takes much too seriously the idea that the Laurence-Moon-Biedl-Bardet syndrome is akin to Status Bonnevie-Ullrich—which Ullrich himself has scouted in this journal. The treatment of the macular dystrophies has been improved. Retrolental fibroplasia (unknown at the time of the first edition) is very well covered, as are "congenital vascular veils in the vitreous," which were apparently also discovered just too late to get into the original work.

In Chaps. VI and VII (iris), one might expect that by now so much "comparative" deadwood would be weeded out, but it is still there (with *gayi* still misspelled *quoyi* in the name of Gay's frog). By now, Miss Mann stands about alone with her view that some vertebrate pigment cells are really mesodermal.

The treatment of the lens and the many forms of cataract (Chap. VIII) is essentially unchanged, but there is a fine insertion on the congenital cataract (and other defects) caused by rubella in the early-pregnant mother. Miss Mann laudably suggests that the condition be named "Gregg's syndrome," after its 1941 discoverer.

The ensuing three chapters, on the cornea (IX), conjunctiva and sclera (X), and adnexa (XI) are essentially unaltered.

The final chapter (XII) on "The Management of Patients with Congenital Abnormalities" is entirely new. The book's dust cover carries a quotation from Conrad Berens's introduction, promising "wise advice concerning the management of patients with congenital anomalies (and their parents)" which is "required reading, not only for ophthalmologists,

but also for psychiatrists and all those interested in handicapped children." This large promise must have been based upon a prospectus, not upon a manuscript of the book, for poor little Chap. XII is barely three pages long. It amounts to a recommendation to have any anomaly-bearing child go ahead and use his eyes (without fear that they will be further damaged), to the best of his brain's ability to interpret what it can see through them.

The most prominent feeling your reviewer had upon putting the book down was that it is a shame that it could not somehow have been integrated with a new edition of Arnold Sorsby's *Genetics in Ophthalmology*. Miss Mann's work does not begin to develop the genetical facts (and plausible fancies) underlying her mass of morphological end-results. The geneticist reader of Sorsby's book finds himself learning a great deal about the inheritance of conditions which are mere names—some of which have not even gotten into the medical dictionaries. The two works make such a beautifully complementary pair, that one may hope that it is premonitory that they have about the same shelf height, thickness, and color of cover! If they are associated in enough libraries, they may sometime be married.

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The Nature and Transmission of the Genetic and Cultural Characteristics of Human Populations

Milbank Memorial Fund, 1957, 141 pages, $1.00.

These ten essays touch on many broad fields of interest to human geneticists.

They are presented in three groups, of which the first inclines towards anthropology. T. Dobzhansky discusses the concept of heredity in man, pointing out that only genes are inherited, that traits and characters are the result of most complex interaction between the three forces, heredity, environment and culture. He emphasizes culture as complicating man's environment in more ways and to greater degrees than Darwinist literature has often appreciated. H. L. Shapiro explains the extraordinary rapidity of human evolution as due to human culture, particularly to its role of reducing the size of gene pools by breaking up our species into large numbers of partial isolates, a situation which is well known to speed up evolutionary processes. He mentions that culture may lessen selection pressures and points out that man may now guide his evolution intelligently to the extent that he is able to modify his culture. R. P. Vance discusses cultural dynamics—the manner in which social characteristics are transmitted from one generation to the next.

The papers in the second group concern the identification, distribution and fertility of people with variant characteristics. W. R. Thompson's paper describes three approaches to the problem of separating genetic from environmental traits in populations. The first, which is felt to be unsatisfactory, involves "culture-free tests"; the second is the multiple variance method of Cattell; the third approach to the problem is actually to sidestep it by concentrating on the phenotypic transmission of psychological characters without being concerned about the relative importance of hereditary and environmental factors. J. F. Jastak and M. Whiteman describe a recent survey of mental retardation in Delaware based on programs of mental and sociological tests of large numbers of subjects, followed by an analysis of the social aptitudes of mentally retarded and non-retarded persons. D. C. Leighton presents data from a mental health survey on the frequency and distribution of persons with psychiatric symptoms in a small town, and the relationship of these symptoms to various socioeconomic features of their particular environment. D. Kirk summarizes a new study of the

fertility of persons listed in "Who's Who in America", a level which has been rising and is now somewhat higher than those of college graduates and professionals, being approximately at the replacement point.

In the third group of papers J. L. Fuller outlines his research on the inheritance of behavior patterns of laboratory animals, comparing them with those of humans. G. Allen discusses the "Genetic Aspects of Mental Disorder", suggesting as a working hypothesis that genetic variation or instability is relatively high in this field because the human brain is phylogenetically new. F. Falkner appraises the potential contribution of longitudinal twin studies, mentioning the chief twin studies of the past, noting the interdisciplinary growth studies now under way in five European countries and the liaison between them, commenting on the future.

While the essays are light reading they are carefully prepared and contain worthy contributions.

RICHARD H. POST
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Columbia University

The Evolution of Human Nature

By C. JUDSON HERRICK. Austin: University of Texas Press, 1956, pp. x + 506, $7.50.

THIS IS a remarkable book and quite a gem for collectors of classics in the behavioral sciences. Broad in conception, beautiful in style, and testamentary in purport, it is written lucidly and concisely, yet contains so much substance that it is difficult to review. Representing the fruits of over sixty years of biological inquiry and reflection, the volume offers a lesson in careful formulation of experimental findings, and a candid summation of the author's philosophy of science and life.

The stated purpose of the book is "to show what some of the available knowledge of human nature means for the guidance of human conduct." Its chief premise is that behavior is both purposive and meaningful. In this "neoteleological" approach, the author aligns himself with men like Sinnot in biology and followers of Hull's teachings in psychology. This school constitutes a reaction to the strictly objective, Helmholtzian treatment of natural science, and parallels the advancement of physics in its abandonment of Newtonian mechanics in favor of Einstein's field theory.

Aiming at reinstating the role of the observer in the scientific scheme, the author denies the existence of "a strictly objective science." In his opinion, "mentalistic factors permeate every inquiry and in the study of human behavior they are crucial." The importance of objective fact-finding is not minimized, but the integration and interpretation of these facts are looked upon as dependent on the subjective mental processes of the scientist. Accumulation of knowledge is seen as subordinate to its interpretation.

The author's approach to the evolution of human behavior is both eclectic and on the holistic side, and generally follows interdisciplinary patterns as proposed by Sherrington, Lashley, Hebb and others. The need for integrating physiological, anatomical, psychological and possibly even sociological data into one all-encompassing frame is continually stressed, yet there is little inclination to underestimate the magnitude of the task involved. Basic concepts of behavior are formulated in such a way as to show a clearly genetic orientation, although no attempt is made to offer specific data on genetics. In some places, one gains the

impression that the assumed equivalence of evolutionary and genetic factors of behavior may have been carried too far.

With neurological theory focused on a nonatomistic understanding of the behavior of the whole organisms in terms of neural activity (with the emphasis on cortical mechanisms), the evolution of thought processes is explained in relation to two primary functions of the nervous system, the analytic and the integrative. By and large, analytic functions depend on stimuli, which impinge on the organism from the outside and are potent enough to precipitate a response. Integrative factors are regarded as (a) intrinsic to the living organism, (b) contingent on cortical activity, and (c) the predominating force in higher animals. In man, they have become such important adaptational forces that the major challenge of adaptation comes from the social environment. With man's survival linked to science (optimum use of integrative capacities), the willingness to point the way to better social adaptation is considered the duty and not merely a privilege of the scientist.

Organizationally, the book can serve as a model. Divided into two major parts (biological and neurological factors in psychobiology), it has 34 chapters, each of which is summarized effectively. The epilogue is entitled "The Unknown God."

The best thing about the volume is its sincerity, the lack of speculative verbosity, the willingness to stand or fall on the reader's faith in science and man. Clearly, it has not been written for cynics. Epitomizing the principle that knowledge is power, but effective knowledge is that which includes knowledge of the limitations of one's knowledge, the book and its author deserve only respect and admiration.

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M. Michael Klaber
New York State Psychiatric Institute

Novant'anni delle Leggi Mendeliane

EDITED BY LUIGI GEDDA. Roma: Instituto Gregorio Mendel, 1956. pp. xxiii and 494. $18.00.

AN EVALUATION of this book, the avowed purpose of which is to commemorate the 90th anniversary of the publication of Mendel's "Versuche über Pflanzen-Hybriden," is a mixed pleasure. One cannot help but admire the book as an example of fine craftsmanship what with the linen and green leather half-binding, the fine quality enameled paper, the excellent color plates, and the formidable task of setting type in no less than six languages—English, Finnish, French, German, Italian, and Japanese. The contents of the book are somewhat less inspiring of admiration.

Novant'anni delle Leggi Mendeliane is divided into three parts. The first part, devoted to Gregor Mendel, the man and his work, consists of the reproduction of his "Versuche über Pflanzen-Hybriden" with an Italian translation, articles by P. C. van Lierde and E. Tschermak on "Carattere e religiosita di Gregorio Mendel" and "Gregor Mendels Versuchstätigkeit und die Zeit der Weiderentdeckung seiner Vererbungsgesetze," and Y. Sinoto's "Nippon ni okeru Mendelism no Hatten to sono oyo." Part II carries the subtitle "Works in General Genetics and in Human Genetics in honor of Gregor Mendel." Ten papers constitute this section; the contributors are A. S. Wiener and I. B. Wexler; W. Lehmann and J. Chelius; J. P. Waardenburg; N. Ford Walker; J. F. Long, L. O. Gilmore, and D. C. Rife; R. Turpin and J. Lejeune; G. C. Schwesinger; H. Harris; W. L. Benedict Nixon; and E. Suomalainen. Finally, Part III, which is subtitled "Works in Medical Genetics, Clinical Genetics, and

Population Genetics in honor of Gregor Mendel," consists of contributions by L. Gedda and G. Iannaccone; W. G. Lennox; C. A. Larson; O. Frhr, v. Verschuer; E. J. Gardner; F. J. Kallmann, B. M. Aschner, and A. Falek; L. Gianferrari, G. Arrigoni, A. Cresseri, G. Lovati, and G. Morganti; H. Kranz; F. C. Fraser; M. Lamy and J. Frezal; J. Francois, F. Gosset, and L. Haustrate; E. Hanhart; M. Weninger; F. Mainx; J. Sutter; and A. A. Maltarello and D. Casa. With so illustrious a list of contributors, one might have expected a truly significant addition to the literature on human genetics. Instead there emerges an extremely uneven and strikingly heterogeneous collection of papers with little to bind them together other than the phrase "in honor of Gregor Mendel."

The weaknesses of *Novant'anni delle Leggi Mendeliane*, while numerous, are not unique; they are merely flagrant illustrations of the abuses of the "Edited by" school of writing.

A paper-by-paper critique of this book can hardly serve a useful purpose nor justify the space since the papers are too numerous and the subjects covered are so many. To indicate something of the unevenness of quality we shall, however, consider several contributions, some of the better and one of the poorer ones. Schwesinger's "Heredity and environment in the development of intelligence" would stand high on any list for the latter distinction. This contribution if not meant to be deliberately patronizing must, then, have been written for presentation to high school students. The statement of the problem, the estimation of genetic and non-genetic components in intelligence, is labored and superficial. The treatment of existing data bearing on this problem reveals neither a special aptness nor originality of thought. The paper is liberally sprinkled with profundities such as "Neither can human beings be grown from slips, in which a part of the parent plant stock is removed and started into a new plant that will have a separate existence," and hyperboles, if they may be honored with this designation, such as "Or like the little fruitfly, *Drosophila melanogaster*, which can produce a new generation of fruit flies within a few hours." Among the better contributions are those of Harris and of Benedict Nixon. Harris's "Genes and enzymes in man" is a paper which many can read with profit. Though no new observations are presented, Harris states in a clear and cogent fashion some of the special problems, difficulties and limitations in the rapidly expanding field of human biochemical genetics. Among the difficulties which he cites are the distinction between abnormalities of intermediary metabolism and renal dysfunction, and the distinction between incomplete metabolic blocks and alternative pathways of metabolism. He particularly stresses the desirability and need for interdigitating direct enzyme studies with metabolic studies lest one arrive too precipitously at the conclusion that the metabolic and clinical features of a particular condition are due to a relative deficiency of a given enzyme. Benedict Nixon's "On the diagnosis of twin-pair ovularity and the use of dermatoglyphic data" is, in effect, a progress report. Nixon's objective is to remedy a statement of Dr. Gordon Allen with reference to dermatoglyphics, namely, they have "a potential usefulness in twin studies that is . . . largely unexplored." He adds his voice to those who have pleaded for the use of objective criteria in appraising zygosity by the similarity method, but contends that methods based on characteristics peculiar to uniovular twins as such provide the only conclusive diagnosis of zygosity. With this none will quibble, but what are these characteristics peculiar to uniovular twins? Nixon seems to believe that some are to be found in dermatoglyphic data. His effort to establish this is not without an element of circularity since his U pairs, presumably monozygotic, are merely twins who could not be shown to be dizygotic. Nixon is, however, to be encouraged in his quest.

This compendium is not entirely without graces. Among these are the papers of van Lierde and Tschermak with their interesting sidelights on Mendel and the rediscovery of his work. Sinoto's history of genetics in Japan coupled with Komai's (*Science* 123: 823–825)

gives a clear insight into the rather amazing amount of work in genetics which has been done in Japan and is largely unknown to persons outside that country. The color plates accompanying Lehmann and Chelius's paper on pigmentation of the iris are as fine as any the reviewer has seen. Suomalainen's work on taillessness in cats and Mainx's survey of recent work on chromosomal polymorphism in natural populations are substantial additions to the literature, but seem strangely out of place in this book which is otherwise devoted to human genetics.

In summary, this book, which could have been a significant contribution, can, in fact, be recommended only to those individuals who collect large books to fill bookshelves more rapidly or to lovers of bibliopegy. Even in these instances, the price will make many potential buyers hesitate.

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LETTER TO THE EDITOR

To the Editor Aug. 6, 1957

Dear Sir:

Permit me this opportunity to comment on the review of my recently released book, *Heredity and Your Life*, Vantage Press, New York; which appeared in the June 1957 issue of the Journal. While the reviewer, H. M. Slatis, makes some favorable remarks, he indicates that he considers the book to be overpopularized and with some of the material inadequately covered. This is the type of reaction so often obtained when an author attempts to do the very important job of presenting a highly technical subject to the general public. I would certainly agree that the book is overpopularized when judged by the standards of writing for human geneticists. Any who have tried writing for the general public, however, would agree that there is a great resistance to any book which gives the appearance of a technical presentation of scientific subjects. The book graveyards are filled with many such books which were excellent presentations of the material covered, but which just did not descend to the level of popularization necessary to attract buyers. While some might consider it a debasement of the ideals of science to use techniques which will attract the average book buyer, I feel that it is better that they be reached this way than not at all. If books on subjects such as human genetics are not written on a popular level by geneticists, they will be written by others with the many errors and misconceptions that are certain to accompany such writings.

I have been happy to note that the great majority of reviewers have been most praising of my efforts. I would not question Dr. Slatis's competence as a geneticist, but feel that if he would consider the purpose of the book more thoroughly and the many problems facing an author in producing such a book, his opinions would more closely coincide with these.

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DeLand, Florida

CORRECTIONS

The following corrections should be made in the paper by Krooth.

Page 173: in the formula following formula (1):

$$\text{FOR: } 16I_j = c\left[\sum_{i=1}^{i=m_j} q_{ij} + 15\left(\sum_{i=1}^{i=m_j} q_{ij}^2\right)\right] + 16(1-c)\left(\sum_{i=1}^{i=m^{j}_{s}} q_{ij}^2\right)$$

$$\text{READ: } 16I_j = c\left[\sum_{i=1}^{i=m_j} q_{ij} + 15\left(\sum_{i=1}^{i=m_j} q_{ij}\right)^2\right] + 16(1-c)\left(\sum_{i=1}^{i=m_j} q_{ij}\right)^2$$

Page 173: in the formula following formula (2):

$$\text{FOR: } k_j = \frac{c\left[\sum_{i=1}^{i=m_j} q_{ij} + 15\left(\sum_{i=1}^{i=m_j} q_{ij}^2\right)\right]}{16I_j}$$

$$\text{READ: } k_j = \frac{c\left[\sum_{i=1}^{i=m_j} q_{ij} + 15\left(\sum_{i=1}^{i=m_j} q_{ij}\right)^2\right]}{16I_j}$$

INDEX FOR BIBLIOGRAPHY OF HUMAN GENETICS 1957

Note: The organization and conventions of this index are tentative. Since most of the papers concern cases or situations which are "congenital," "genetic," "hereditary," or "idiopathic," such words as these are frequently omitted. Readers are invited to comment on any aspect of the index, addressing their communication to Dr. R. H. Post, Quogue, Long Island, New York. The numbers on the right indicate the serial positions of titles in the Bibliography published in Vol. 9.

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